Контактная сигнализация

с/к «Межклеточная коммуникация»

Лекция 4

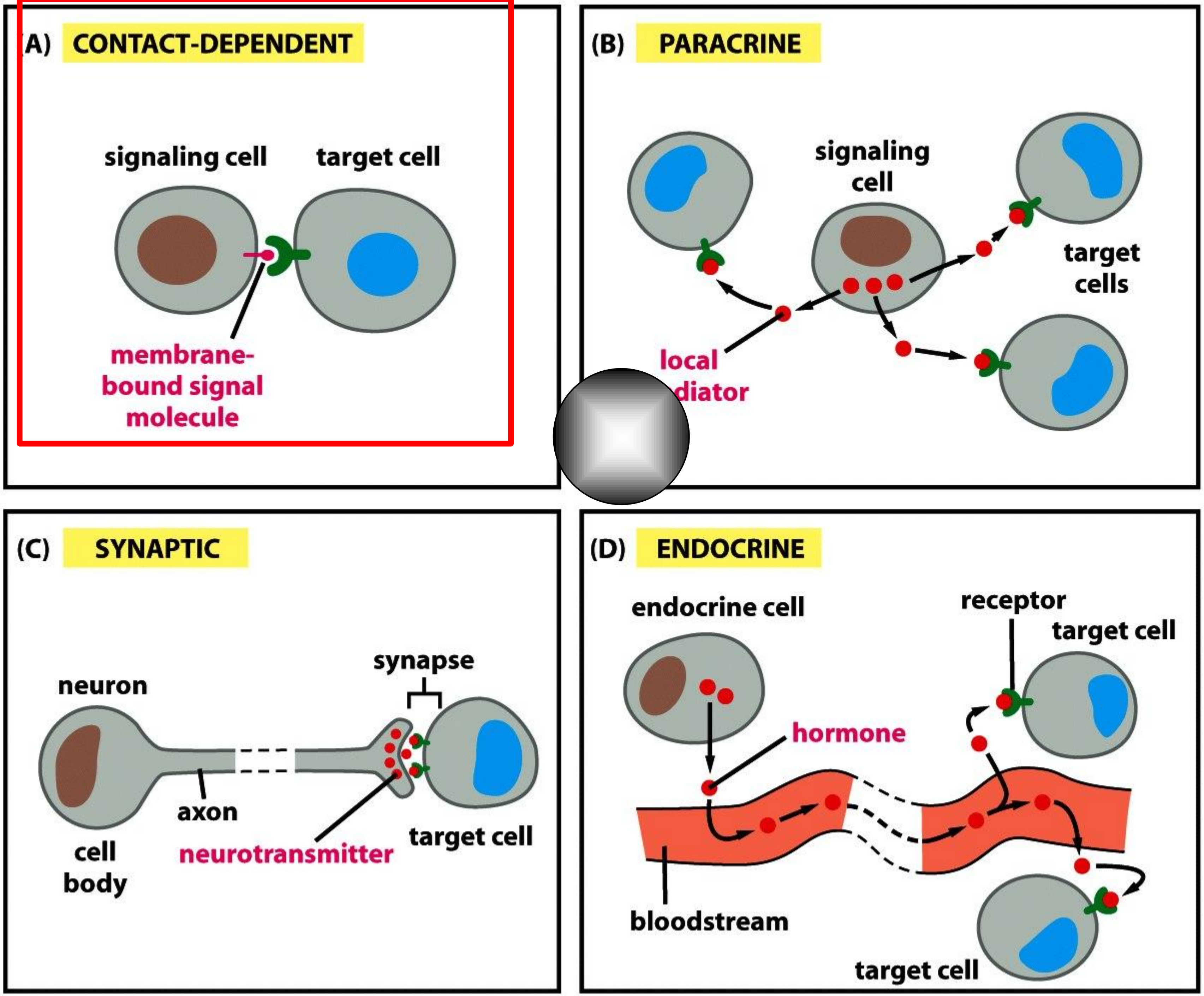
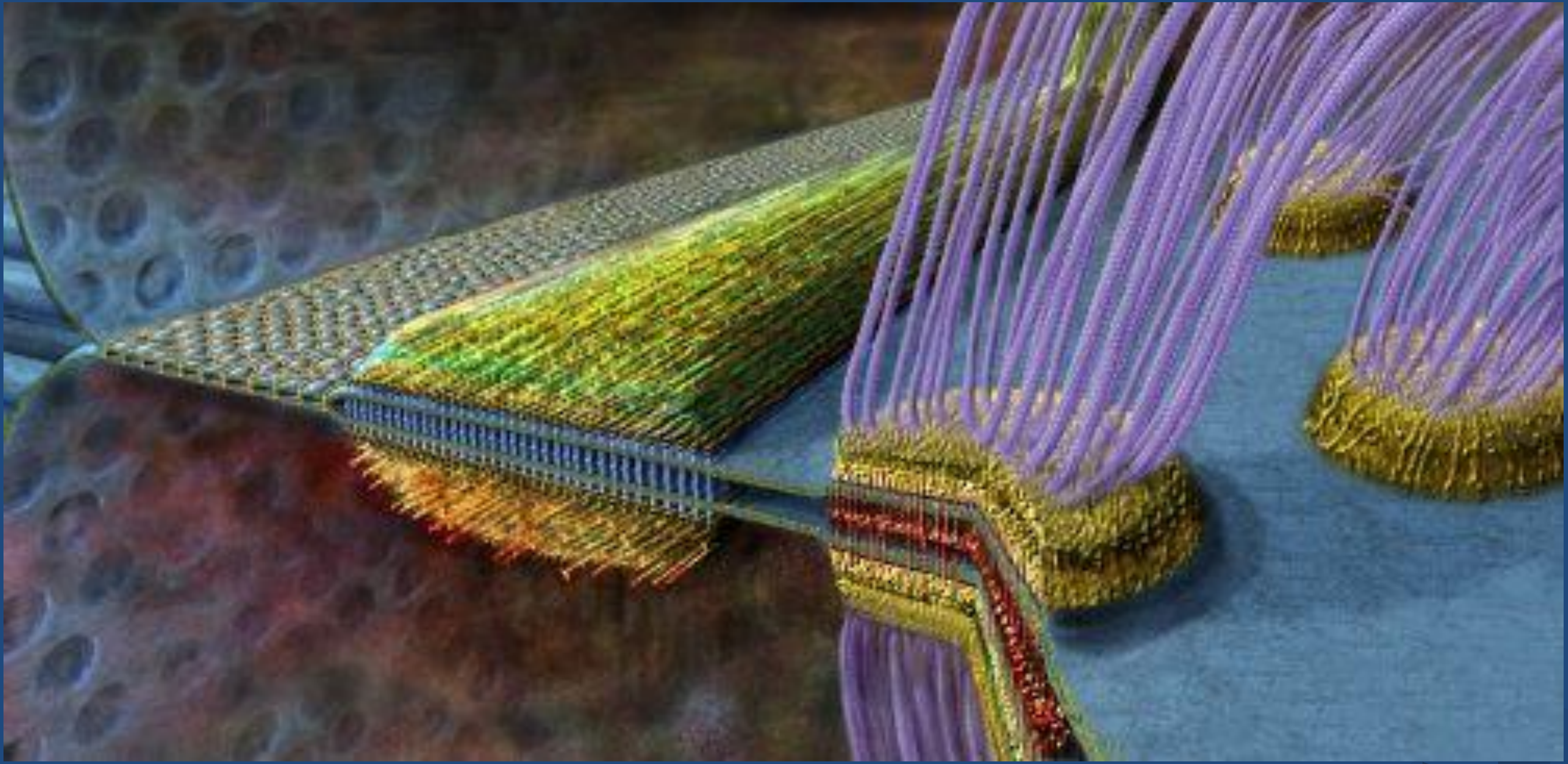
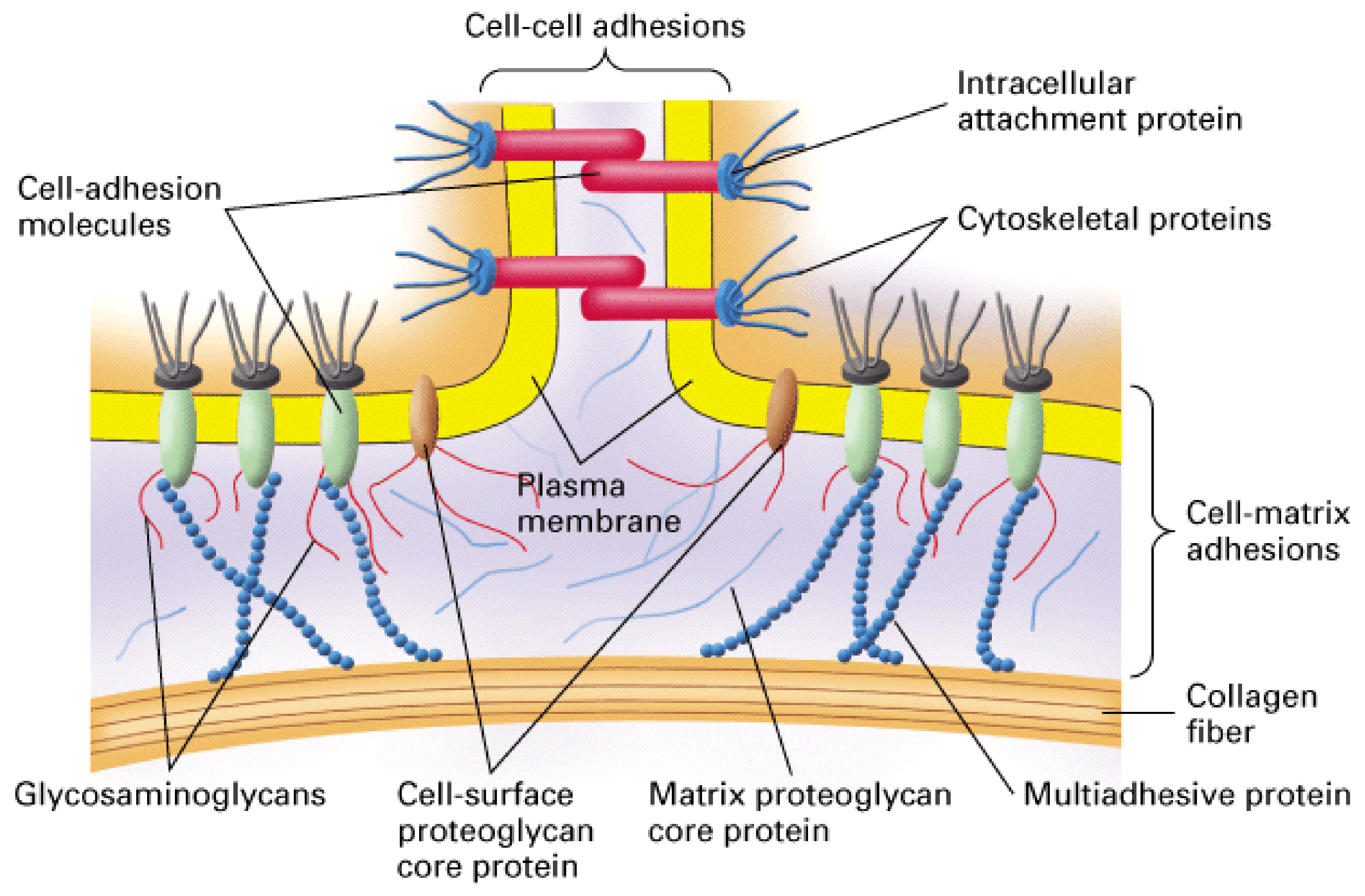


Figure 15-4 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Cell Junctions



Контакты клетка-клетка, клетка-матрикс

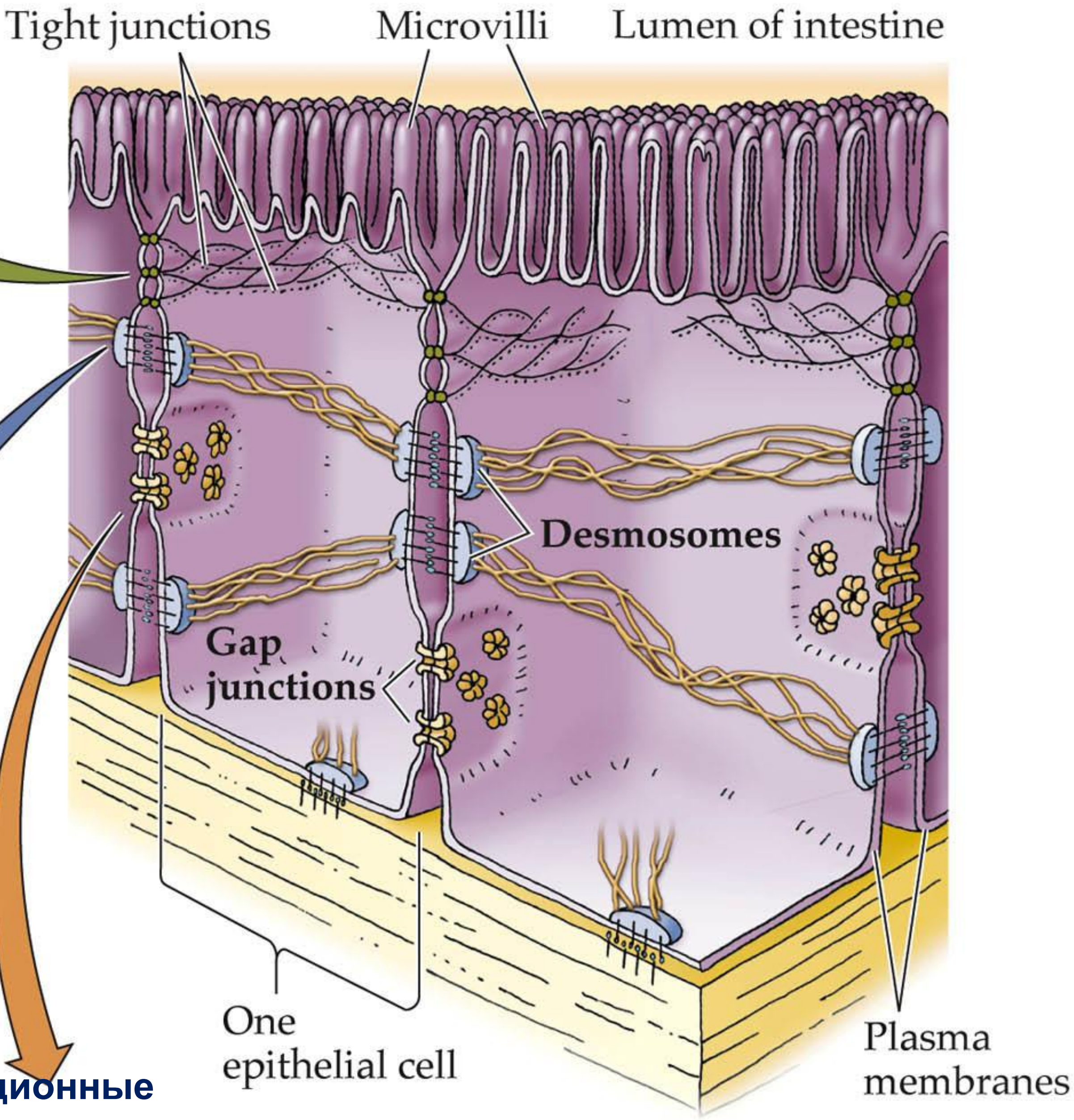


Cell Junctions

Замыкающие контакты

Прикрепительные контакты

Коммуникационные соединения



LIFE: THE SCIENCE OF BIOLOGY, Seventh Edition, Figure 5.6 Junctions Link Animal Cells Together (Part 1)

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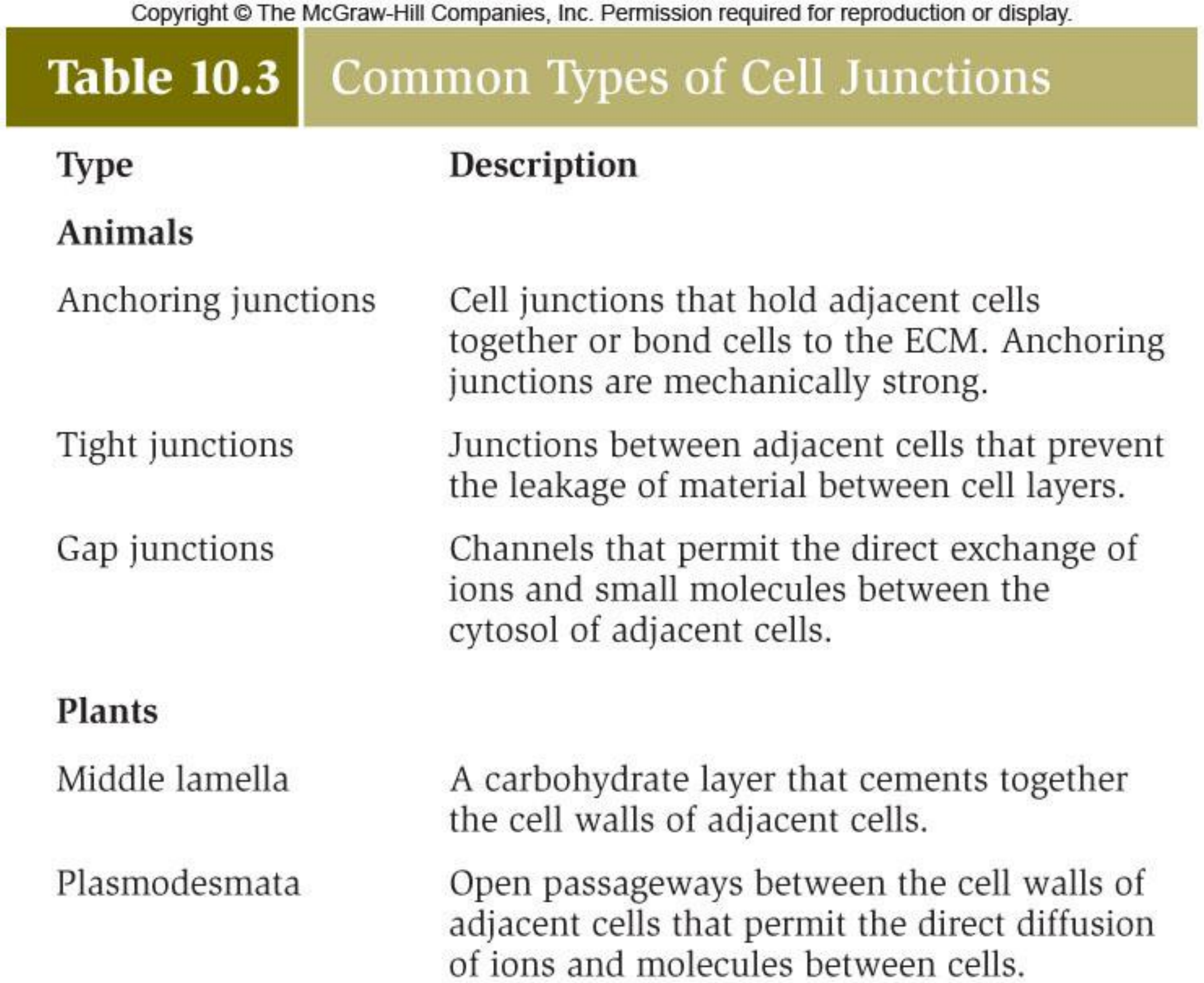

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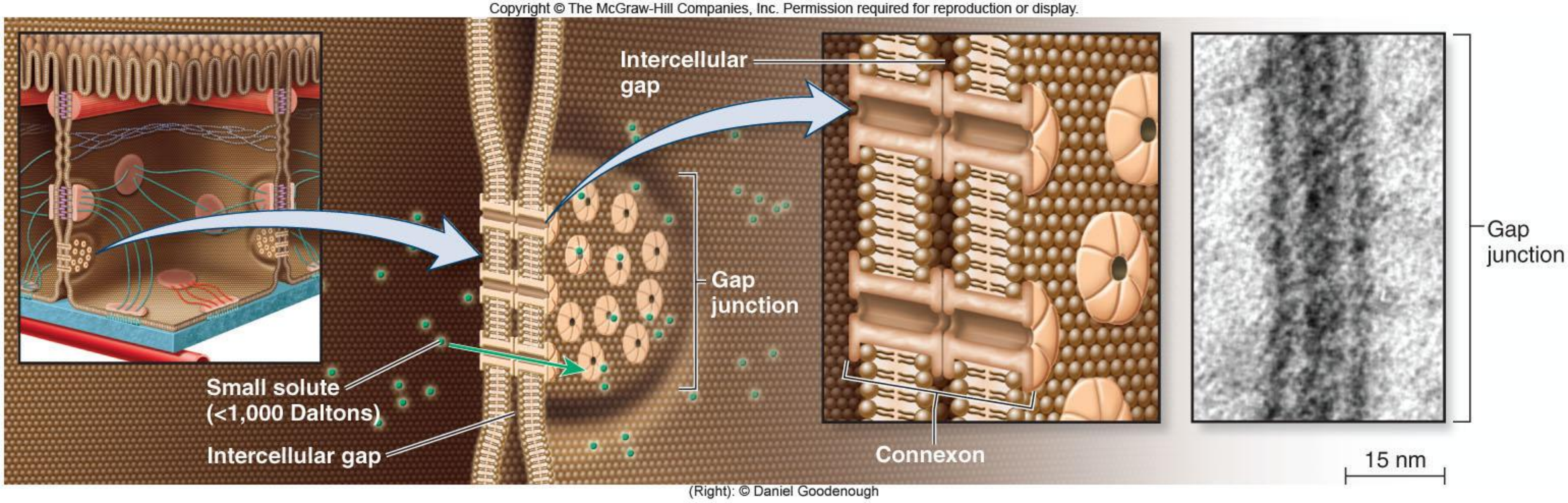
Table 10.3 Common Types of Cell Junctions

Type	Description
Animals	
Anchoring junctions	Cell junctions that hold adjacent cells together or bond cells to the ECM. Anchoring junctions are mechanically strong.
Tight junctions	Junctions between adjacent cells that prevent the leakage of material between cell layers.
Gap junctions	Channels that permit the direct exchange of ions and small molecules between the cytosol of adjacent cells.
Plants	
Middle lamella	A carbohydrate layer that cements together the cell walls of adjacent cells.
Plasmodesmata	Open passageways between the cell walls of adjacent cells that permit the direct diffusion of ions and molecules between cells.

Gap Junctions

Connecting cells by "large pipes"

- Allow small ions to pass ***between*** cells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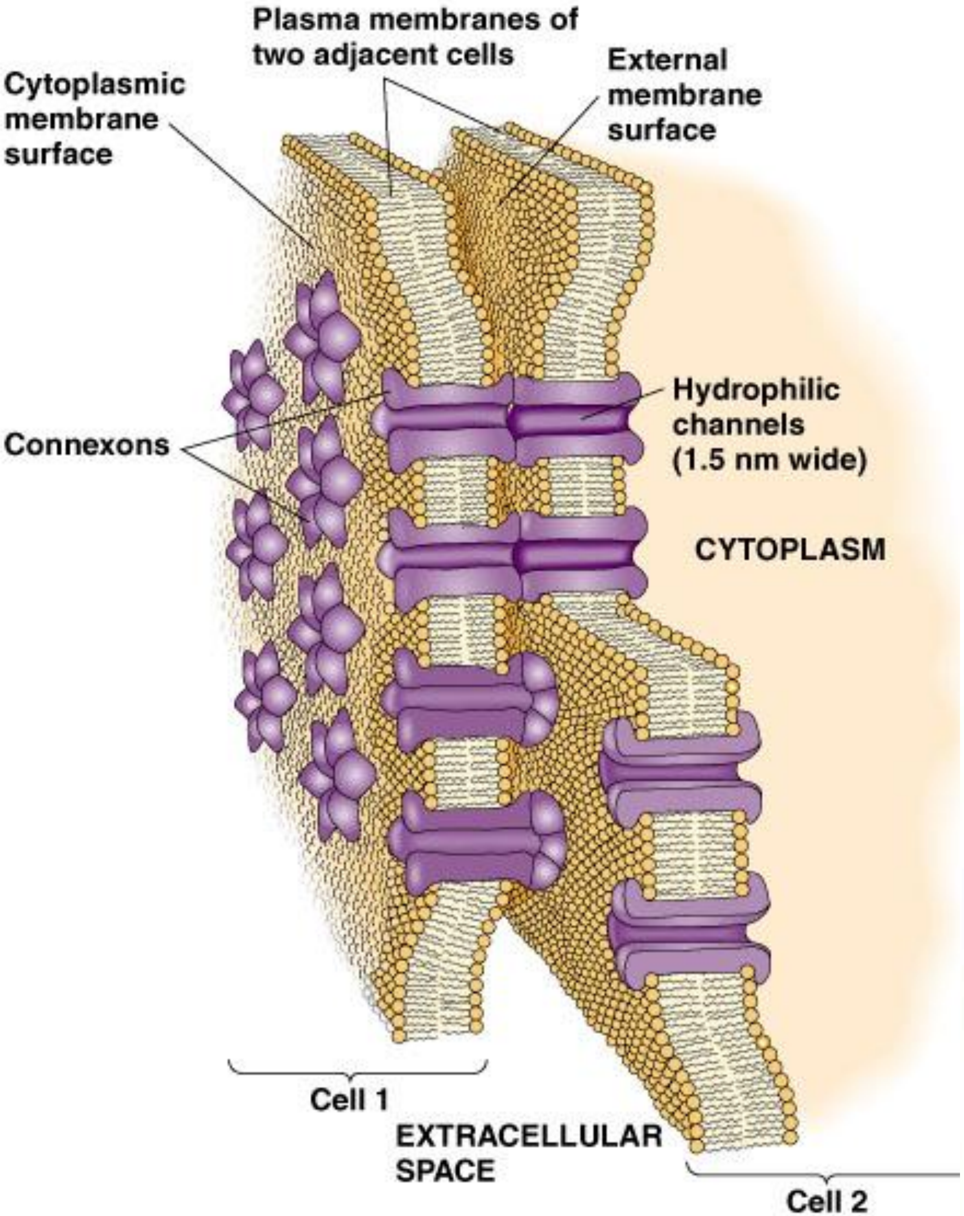
Plasma membranes of two adjacent cells
Cytoplasmic membrane surface
External membrane surface
Connexons
Hydrophilic channels (1.5 nm wide)
CYTOPLASM
Cell 1
EXTRACELLULAR SPACE
Cell 2

(a) Gap junction diagram

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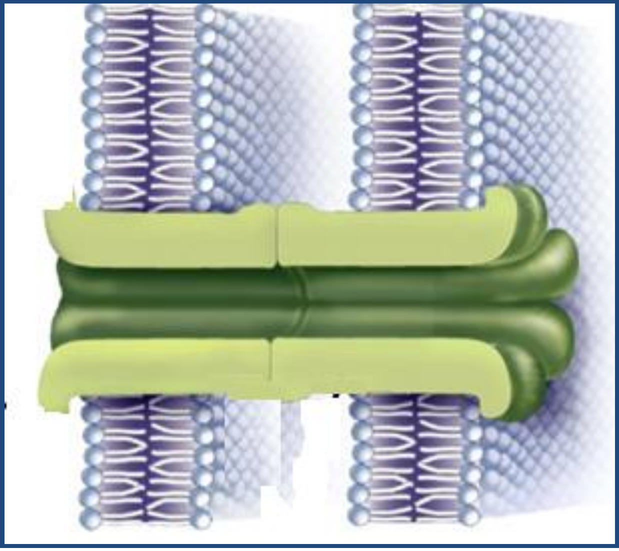

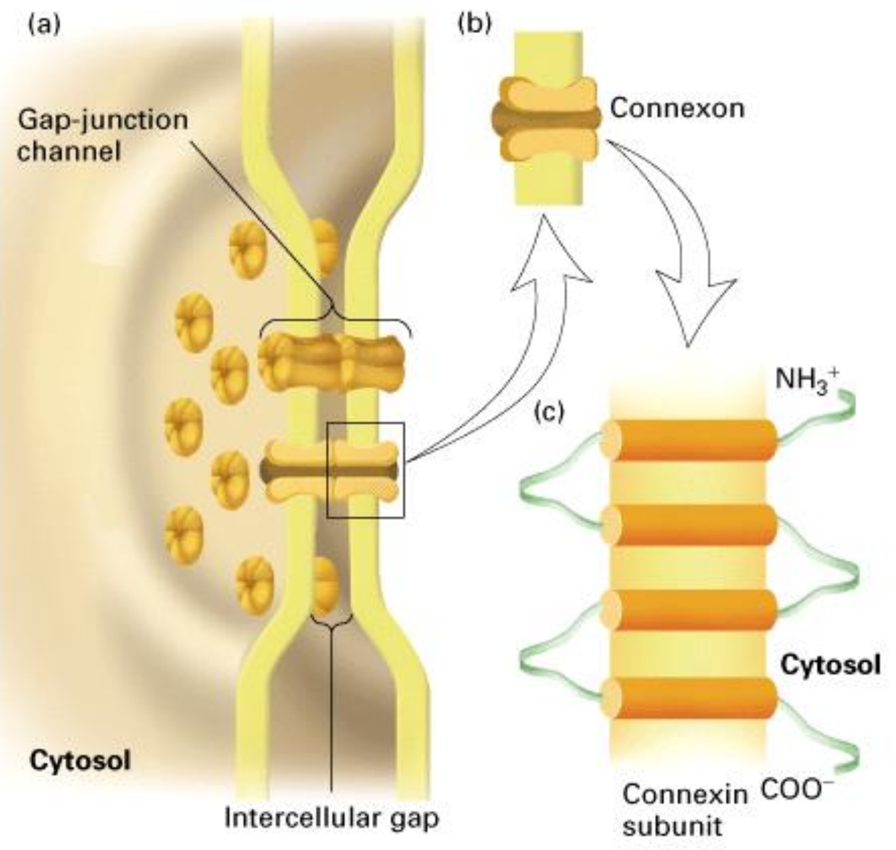

Plasmodesmata create gaps that connect plant cells.

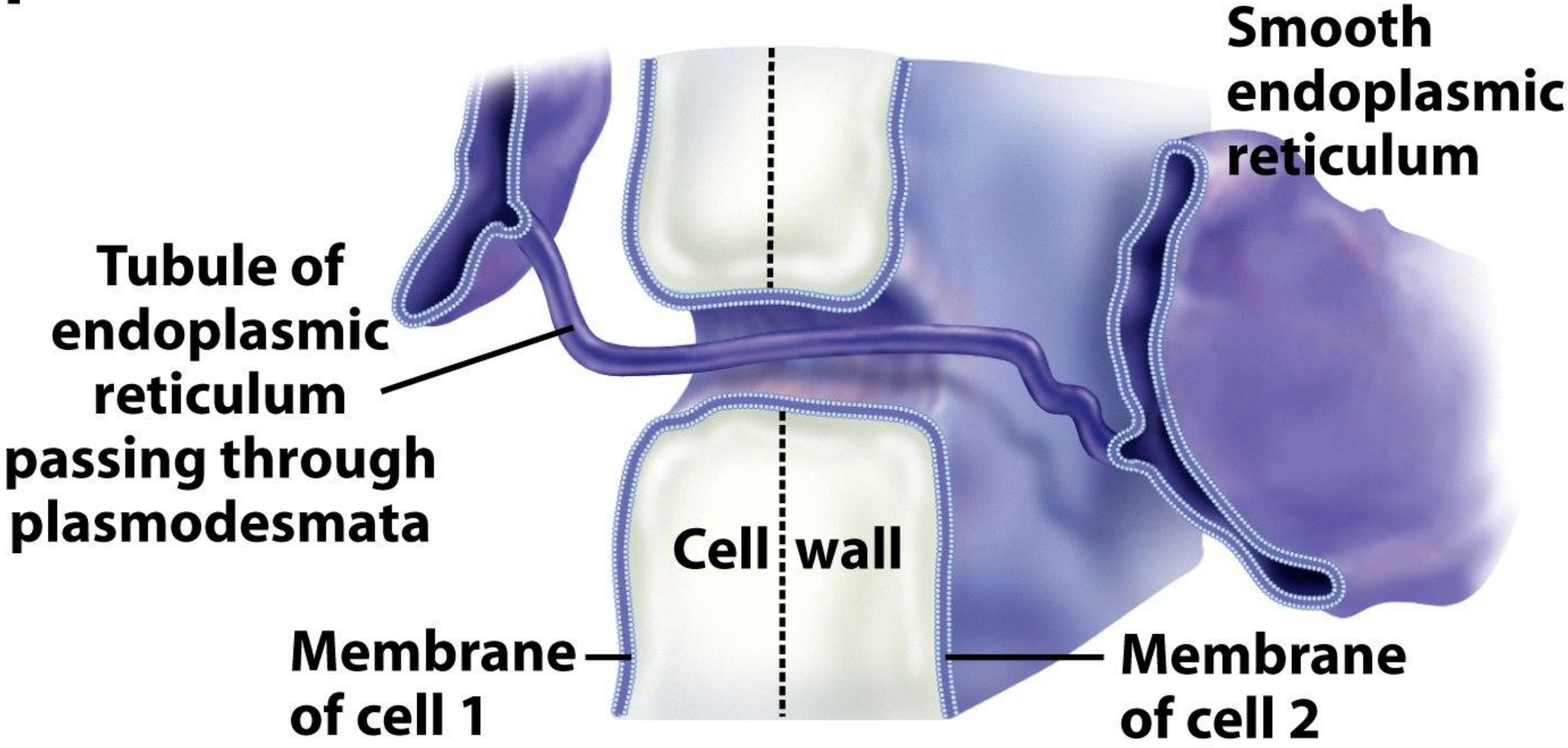
Smooth endoplasmic reticulum
Tubule of endoplasmic reticulum passing through plasmodesmata
Cell wall
Membrane of cell 1
Membrane of cell 2

Figure 8-13a part 2 Biological Science, 2/e

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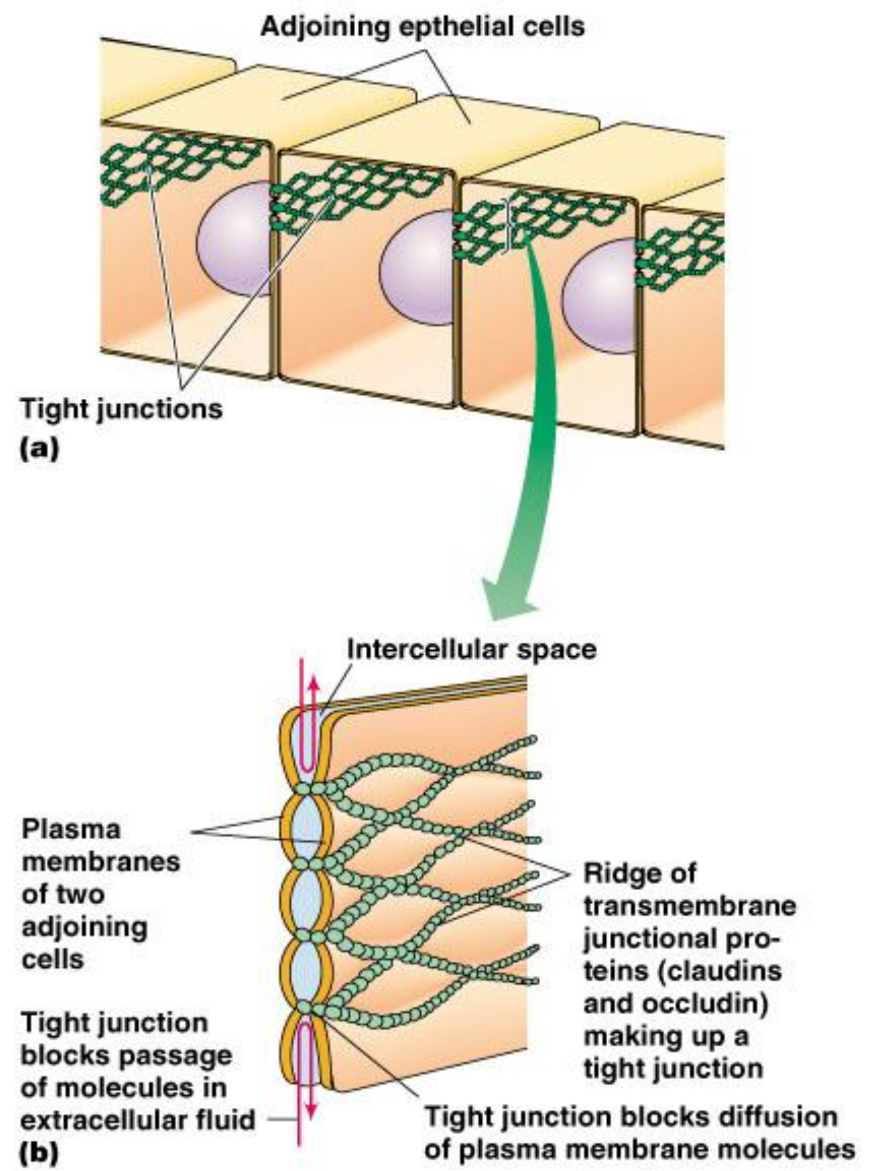
- Large channels (20-40 nm wide) between plant cells
- Allow movement of small molecules across the plasma membrane and cell wall

Tight Junctions

- Tight junctions hold cells very tightly together; solutes cannot pass around cells
- Cells connected by tight junctions seal off body cavities
  - blood/brain barrier
    - spinal fluid/blood
  - Pericardial cavity
  - Peritoneum

Holding cells together by "zippers"


Adjoining epthelial cells
Tight junctions
(a)
Intercellular space
Plasma membranes of two adjoining cells
Ridge of transmembrane junctional proteins (claudins and occludin) making up a tight junction
Tight junction blocks passage of molecules in extracellular fluid
(b)
Tight junction blocks diffusion of plasma membrane molecules

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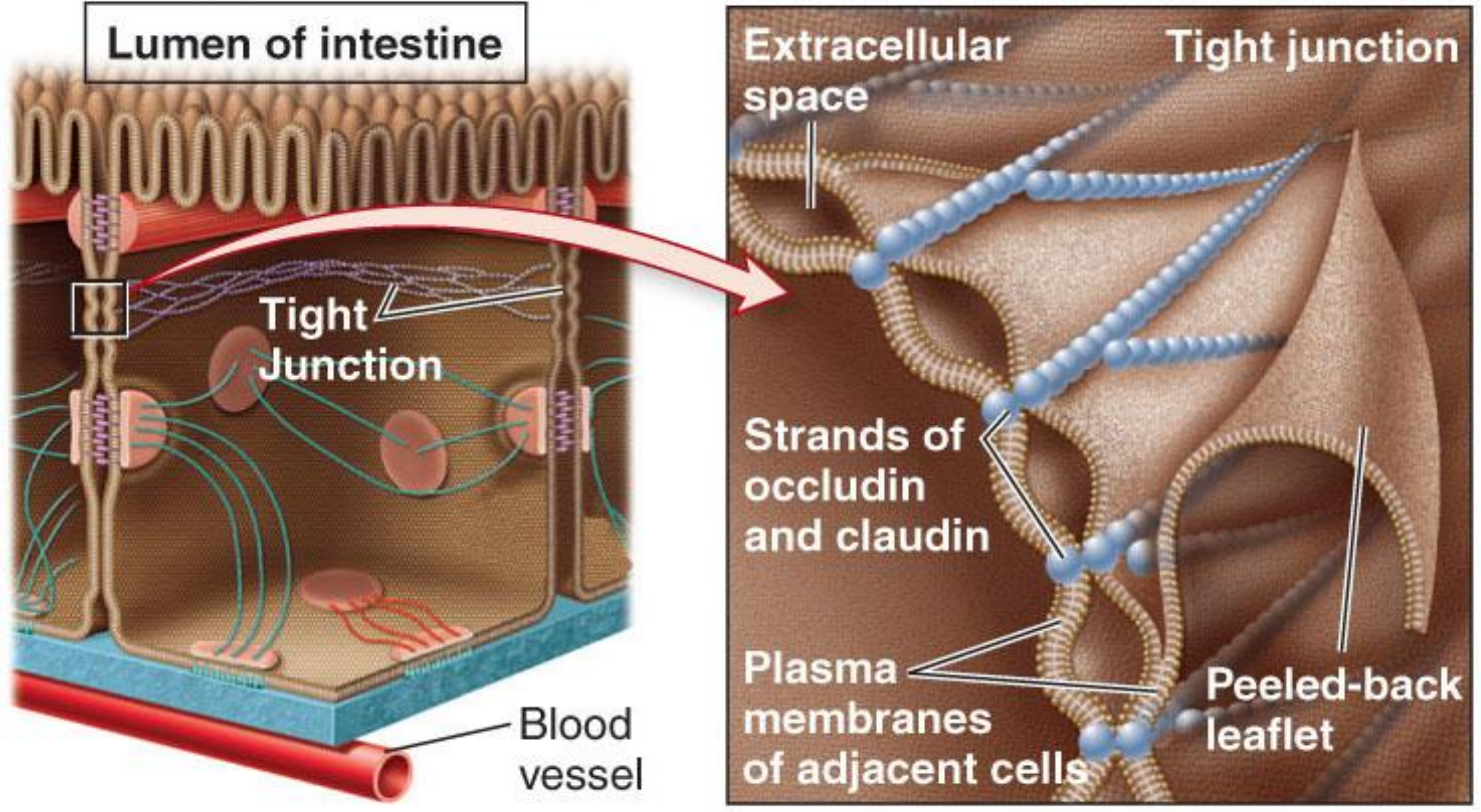
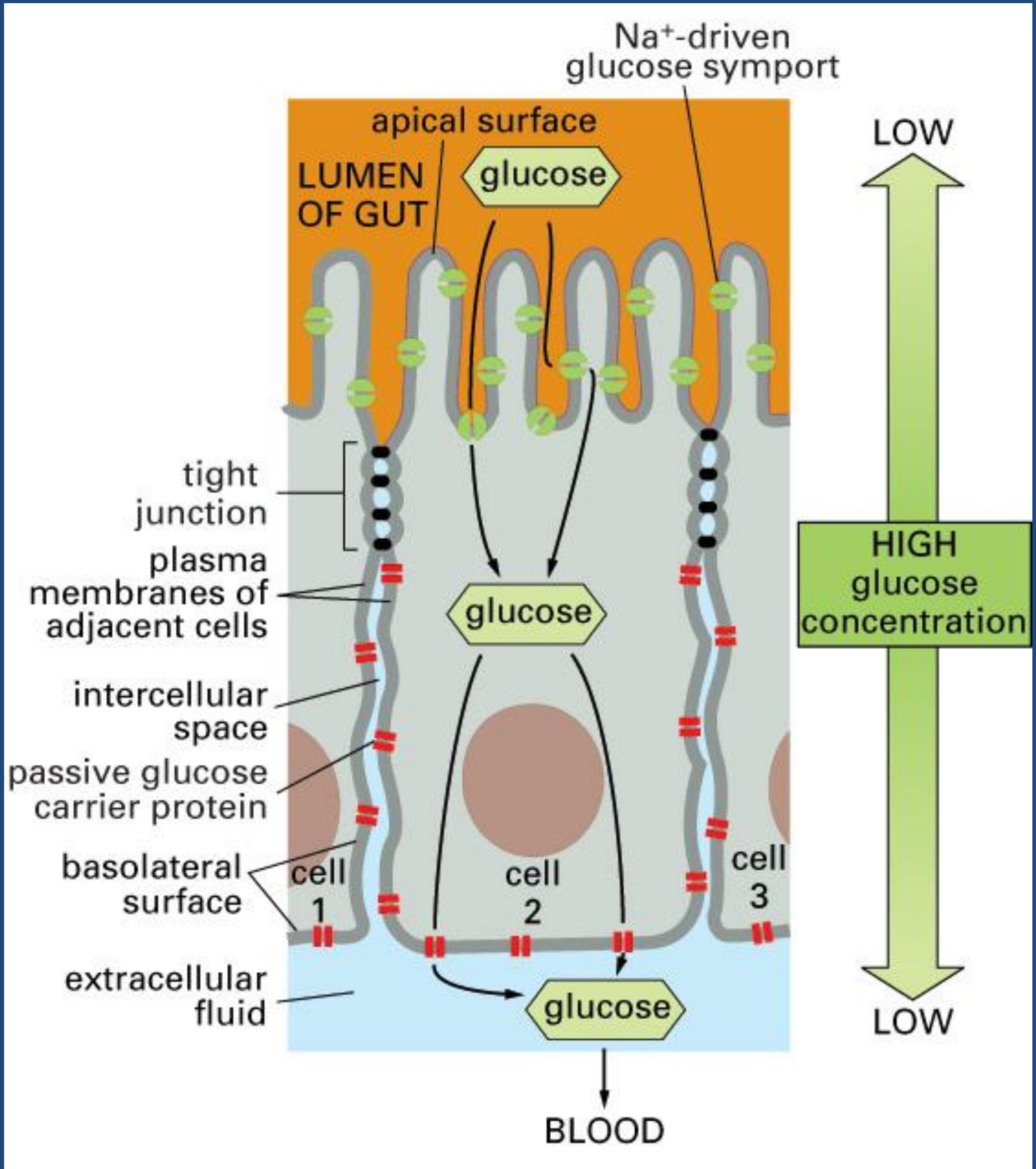


Cells Stick Together by Tight Junctions



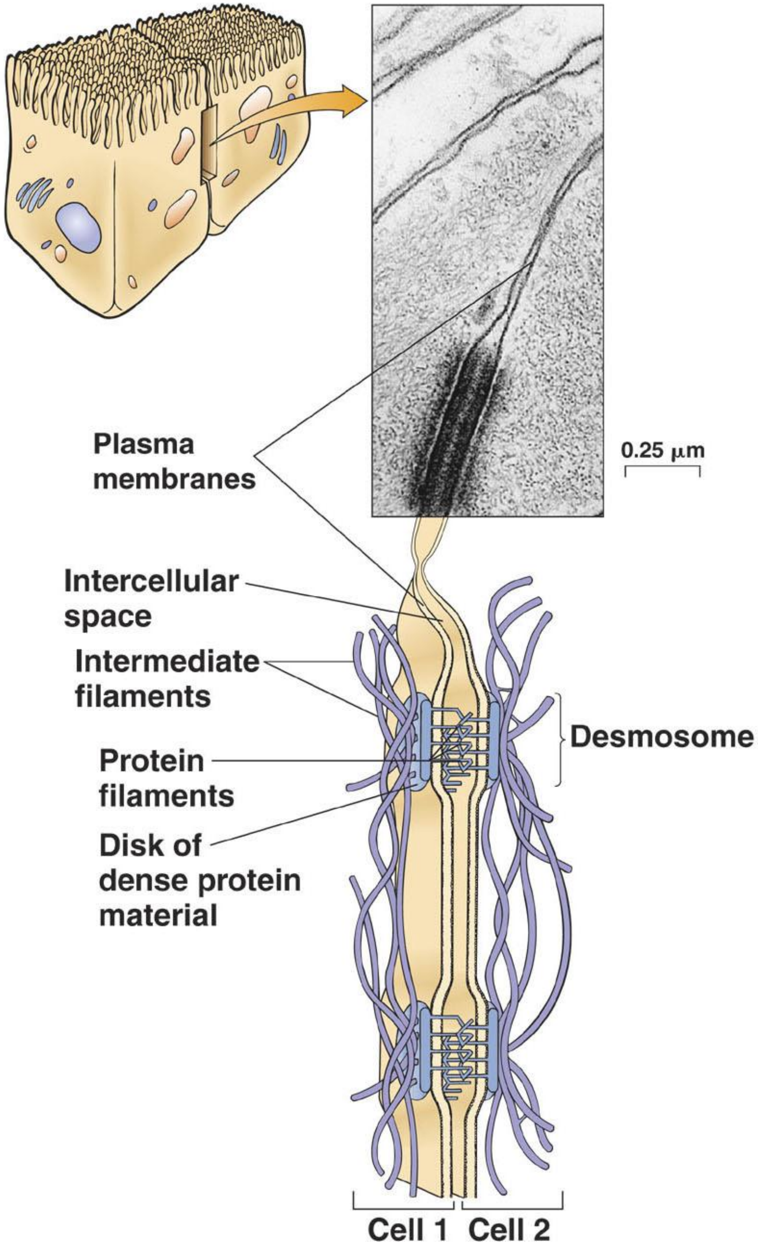
Prevent Membrane Protein and Lipid Diffusion

Desmosomes

- Desmosomes are points of attachment betweencells.
  - Intermediate filaments anchor the desmosomes in cell.

Holding cells together by “snaps”

Solomon/Berg/Martin, Biology, 6/e
Figure 5.22



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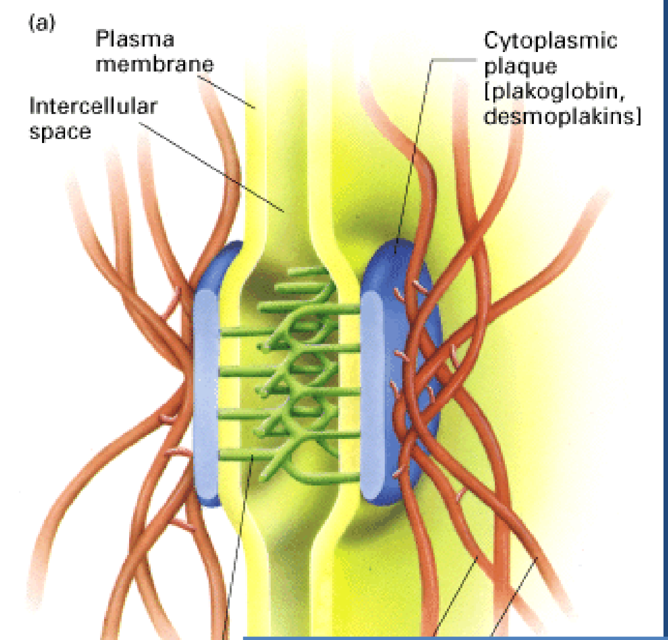
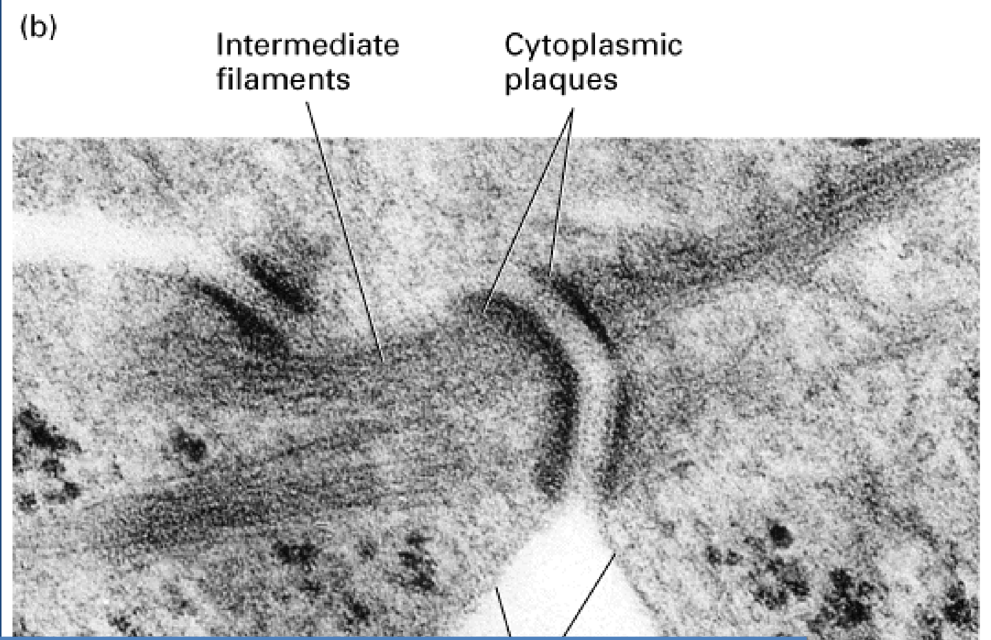
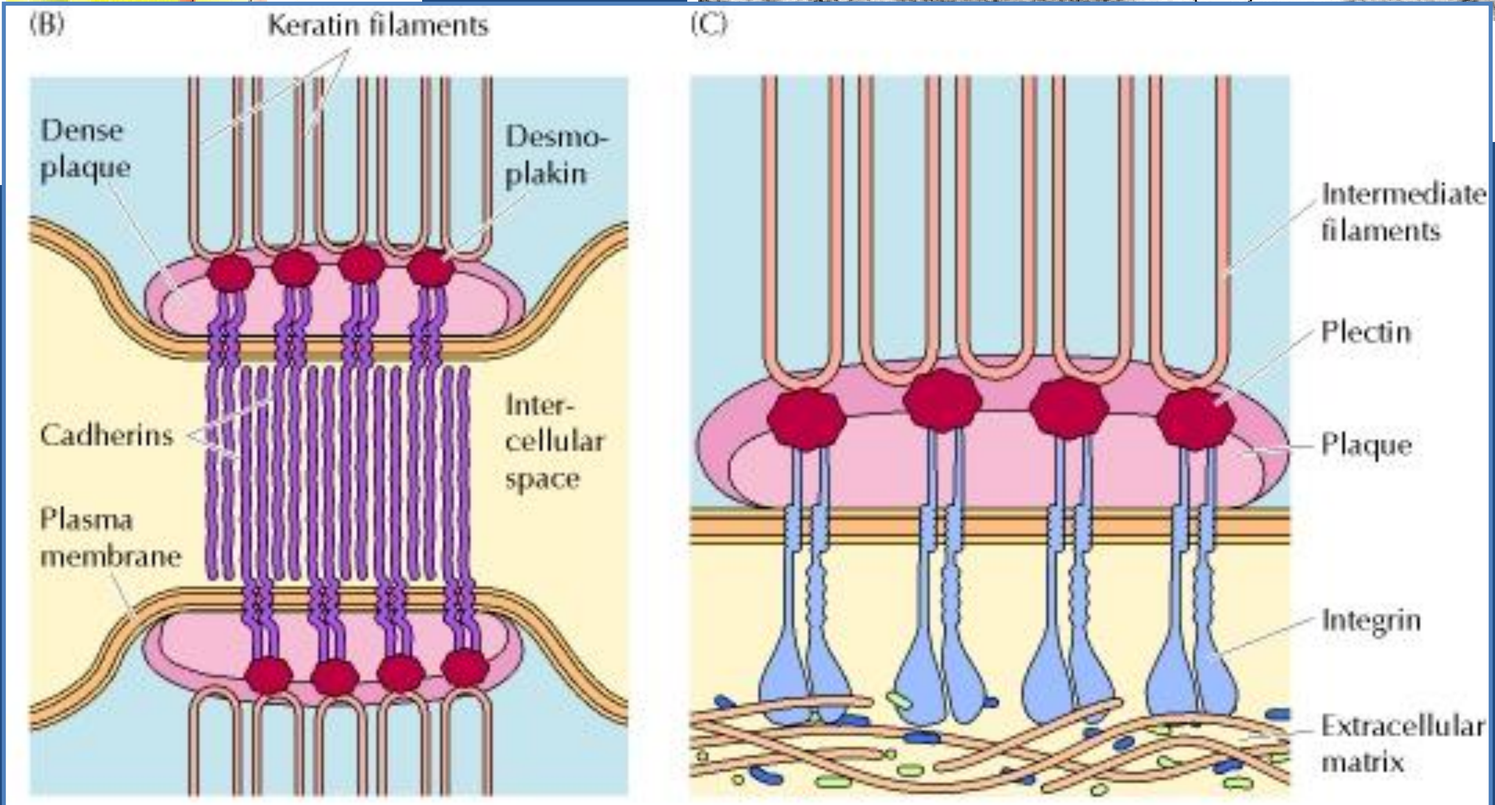
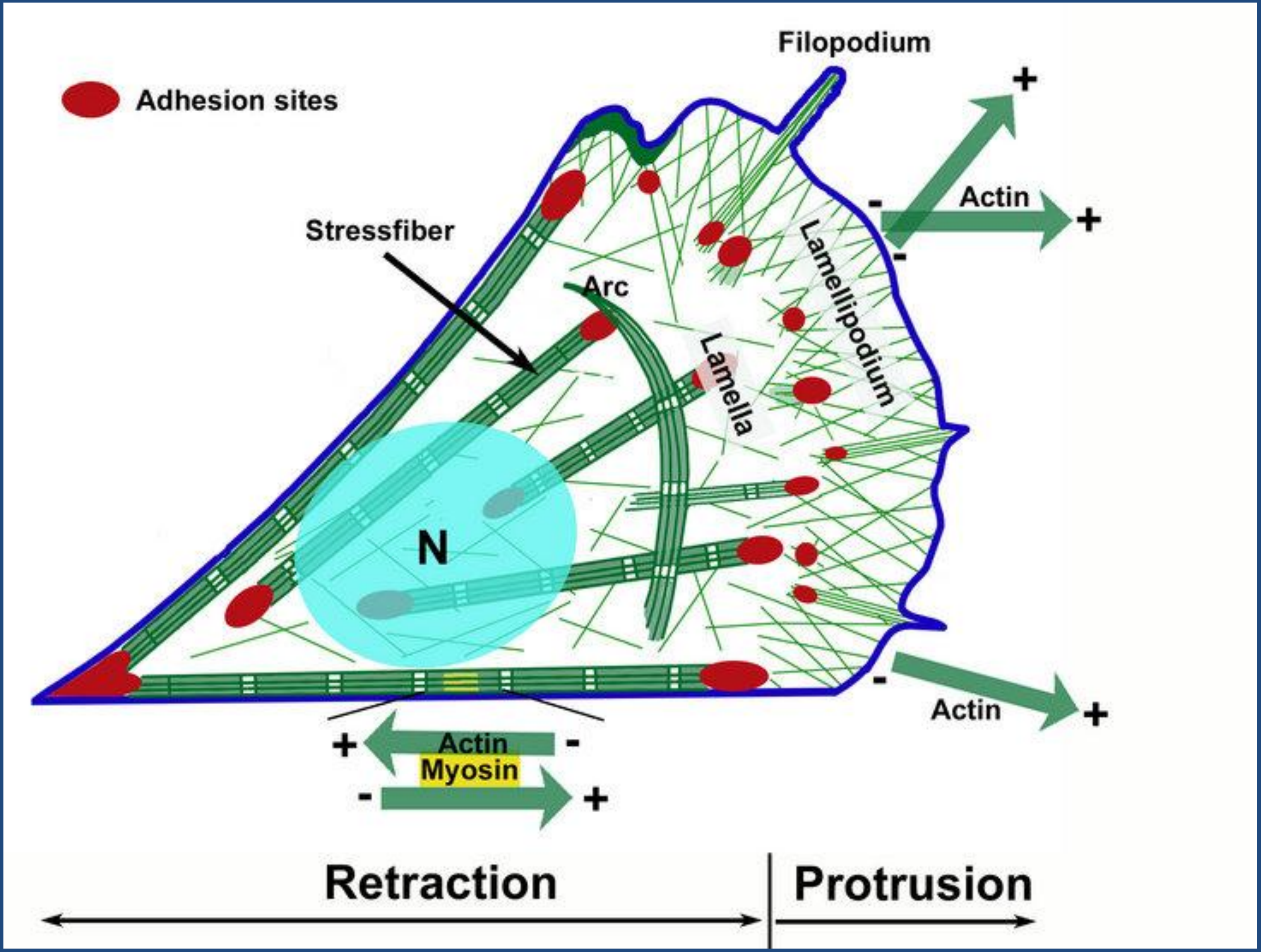

(a)
Plasma membrane
Intercellular space
Cytoplasmic plaque [plakoglobin, desmoplakins]
Desmoglein and desmocollin (cadherins)

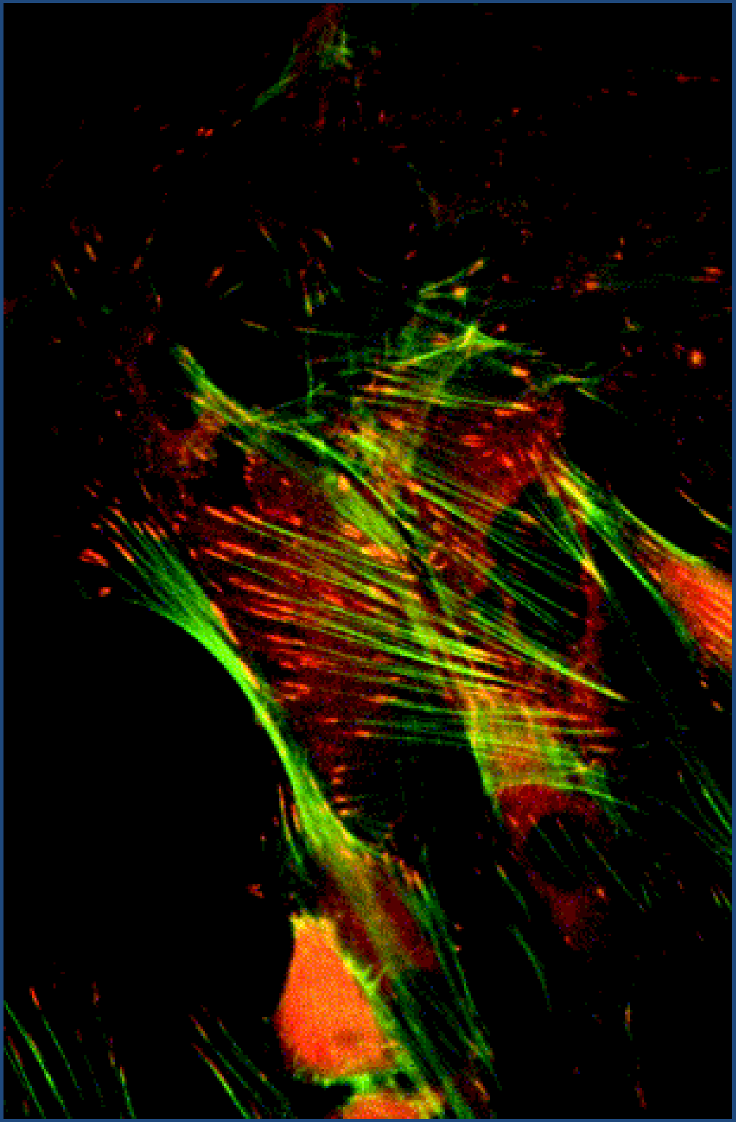

(b)
Intermediate filaments
Cytoplasmic plaques
0.2 μm


(B)
Keratin filaments
Dense plaque
Desmoplakin
Cadherins
Intercellular space
Plasma membrane
(C)
Intermediate filaments
Plectin
Plaque
Integrin
Extracellular matrix

Варианты расположения актиновых филаментов в клетке (фибробласт) в ходе ее движения



Focal Adhesions & Stress Fibers



Petit & Thiery, Biology of the Cell, 92 (2000), 477-494

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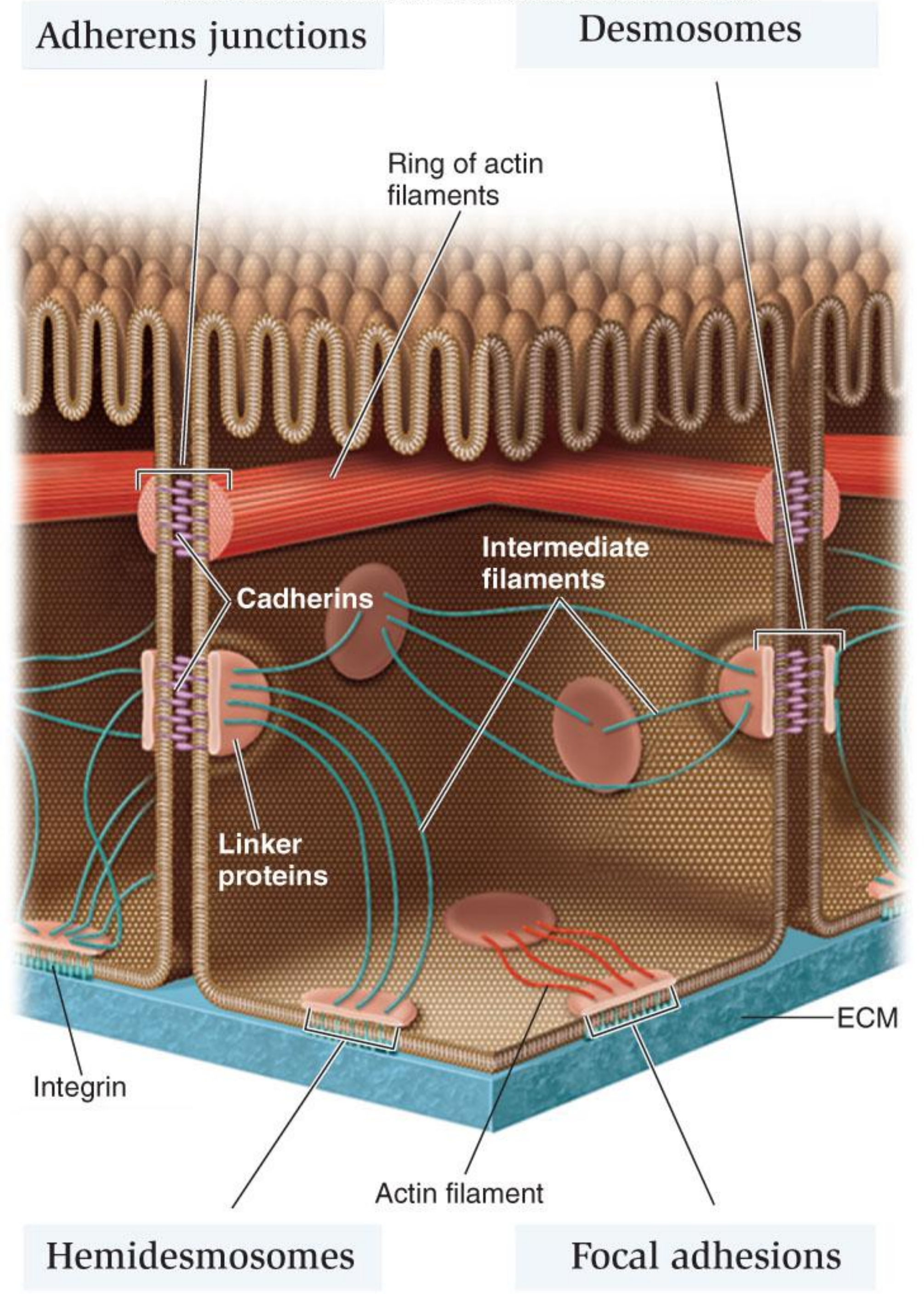


- In desmosomes, cadherins connect cells to each other and to intermediate filaments

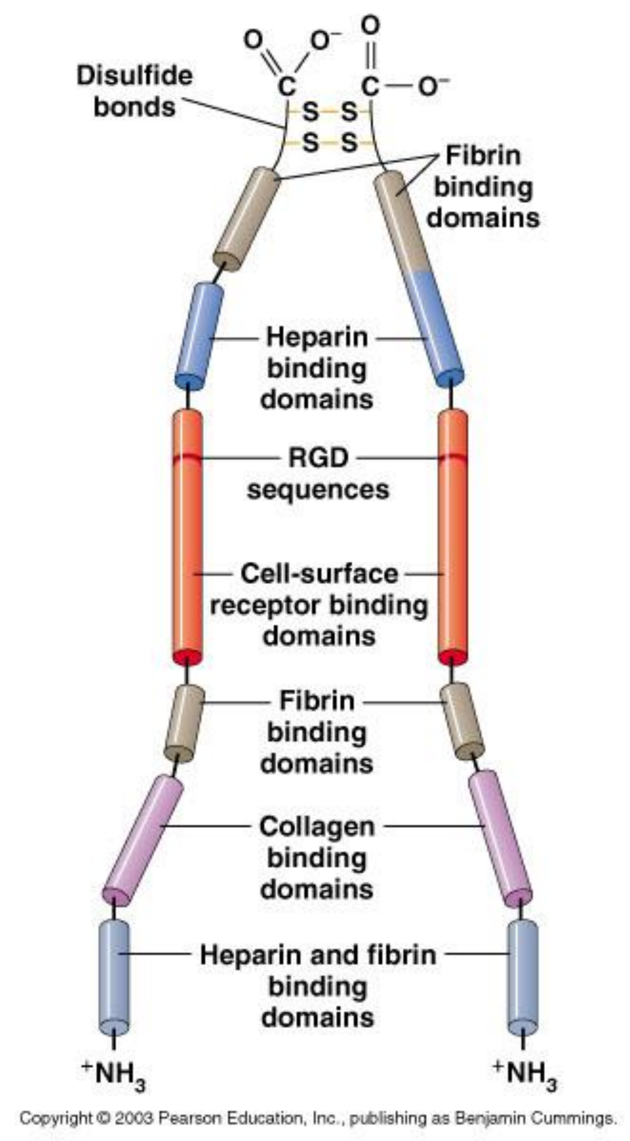
Major components of the ECM

PROTEOGLYCANS
(glycosaminoglycans linked to proteins)

Structure proteins:
COLLAGEN
ELASTIN

Adhesive proteins
FIBRONECTIN
LAMININ, etc

Адгезивные белки ВМ: фибронектин и ламинин



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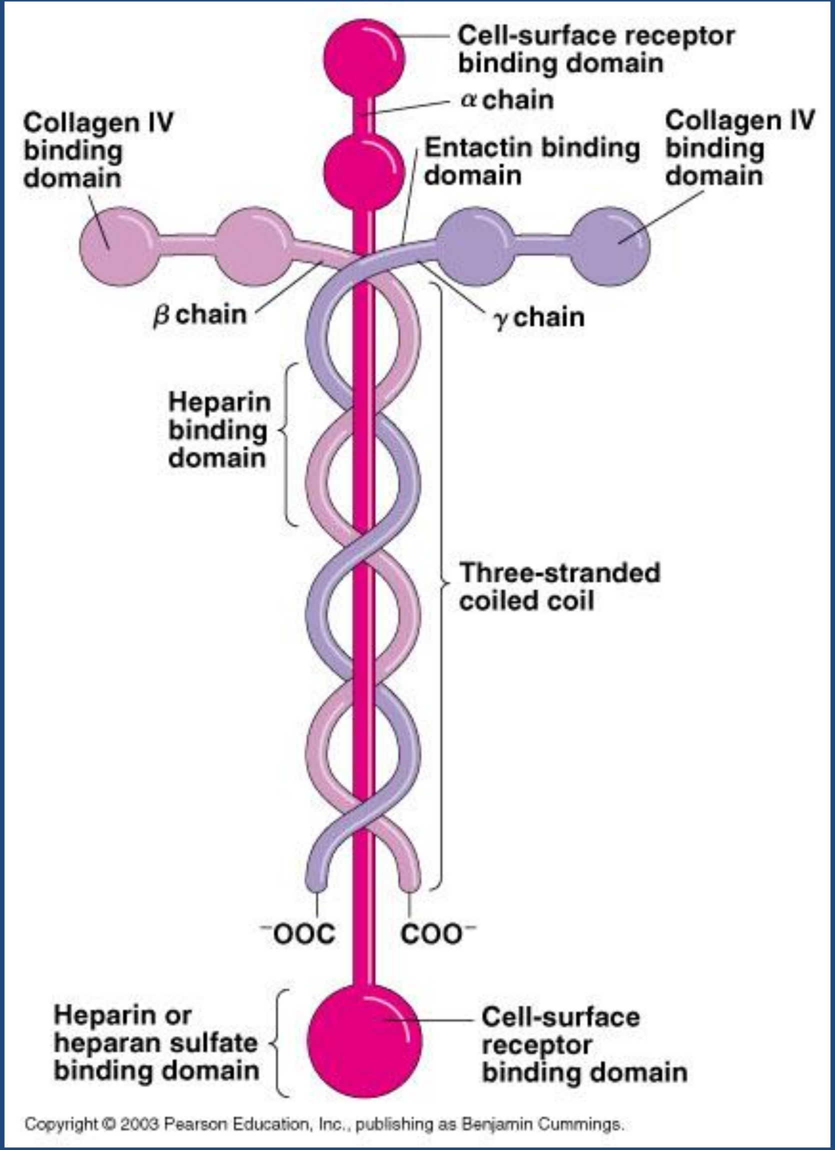
Cell-surface receptor binding domain
α chain
Collagen IV binding domain
Entactin binding domain
Collagen IV binding domain
β chain
γ chain
Heparin binding domain
Three-stranded coiled coil
⁻OOC
COO⁻
Heparin or heparan sulfate binding domain
Cell-surface receptor binding domain

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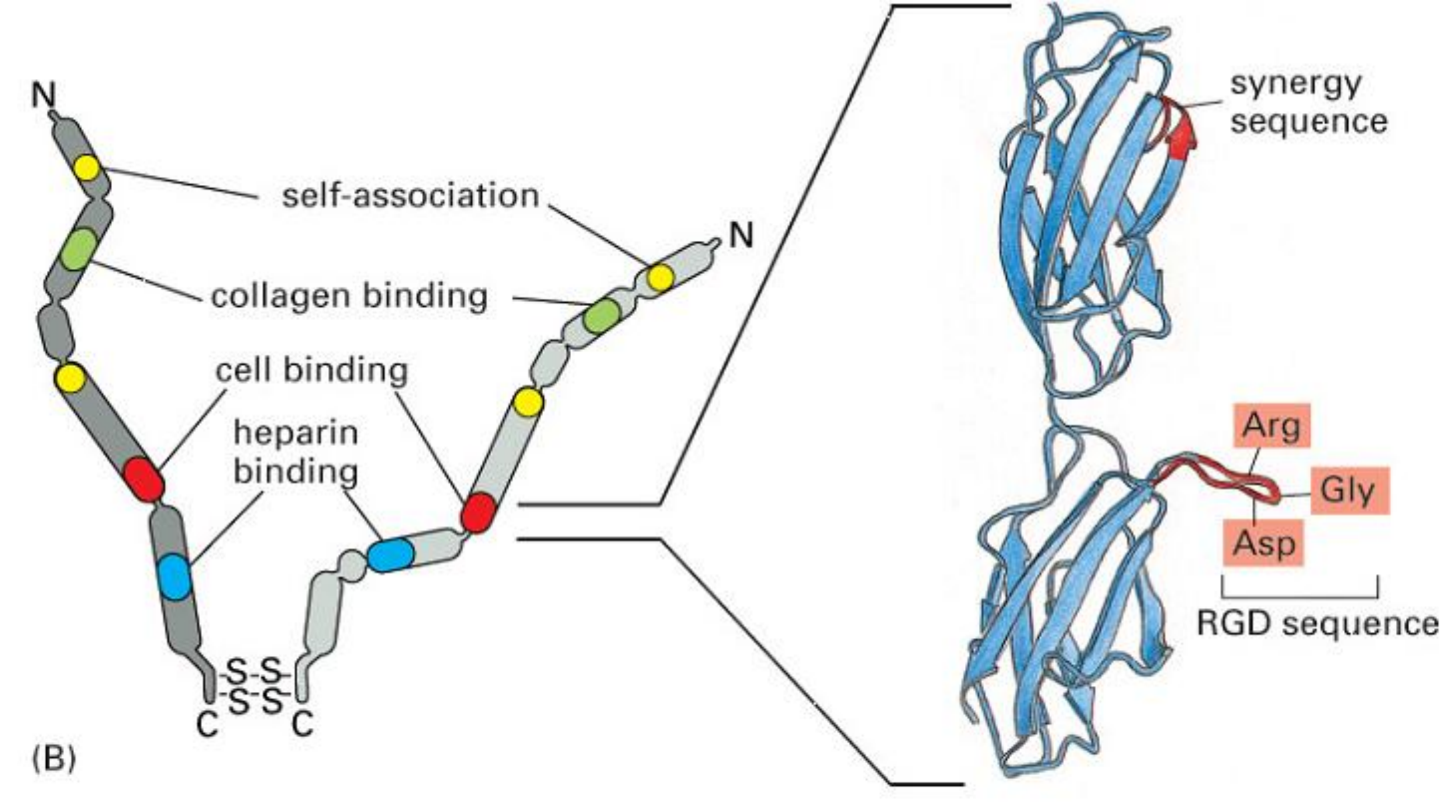
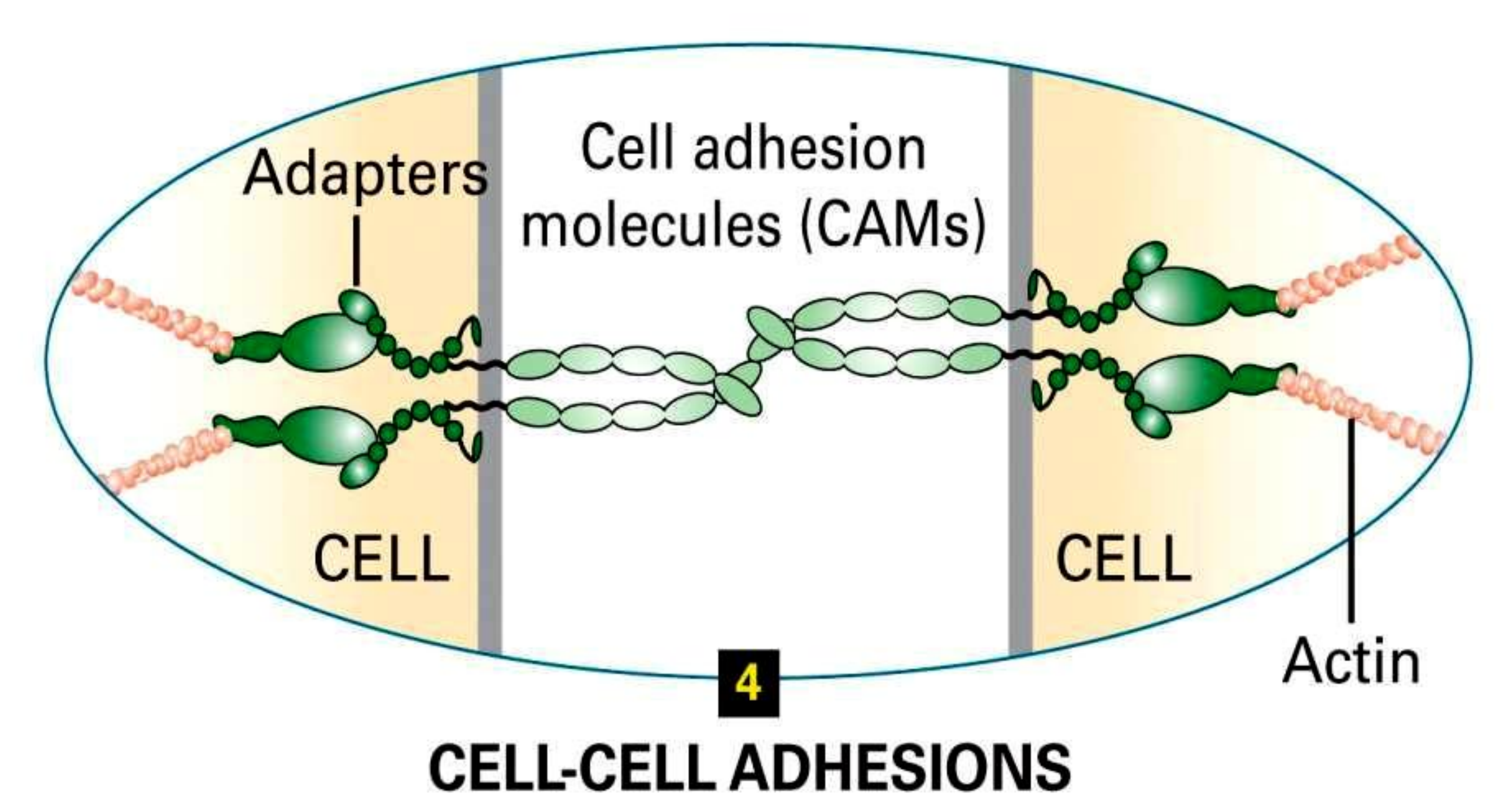
Structure of Fibronectin



Cell-adhesion molecules (CAMs)

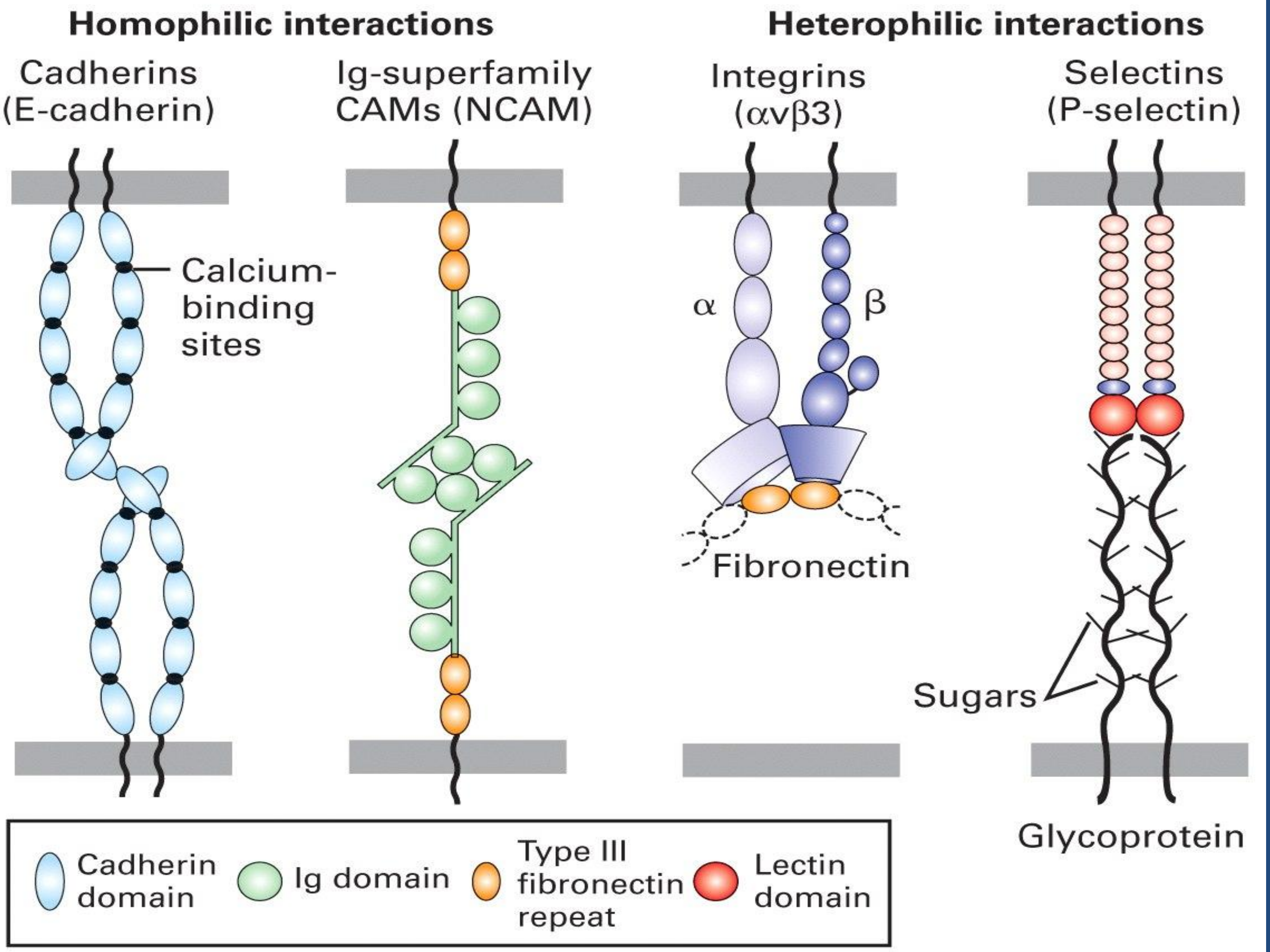
– mediating cell–cell adhesions



- **4 Major families**: Cell-Adhesion Molecules (CAM)
  1. **cadherins**
  2. **immunoglobulin (Ig) superfamily**
  3. **integrins**
  4. **selectins**

- **Type of adhesion**: based on extracellular domains
  - ***Homotypic* adhesion** : **between cells of the same type,** *homophilic* binding
  - ***Heterotypic* adhesion** : **between cells of different types,** *heterophilic* binding

- **Functions: as cell junctions**
  - Cytosol-facing domains recruit sets of multifunctional adapter proteins
  - Control **protein activity** and **gene expression**

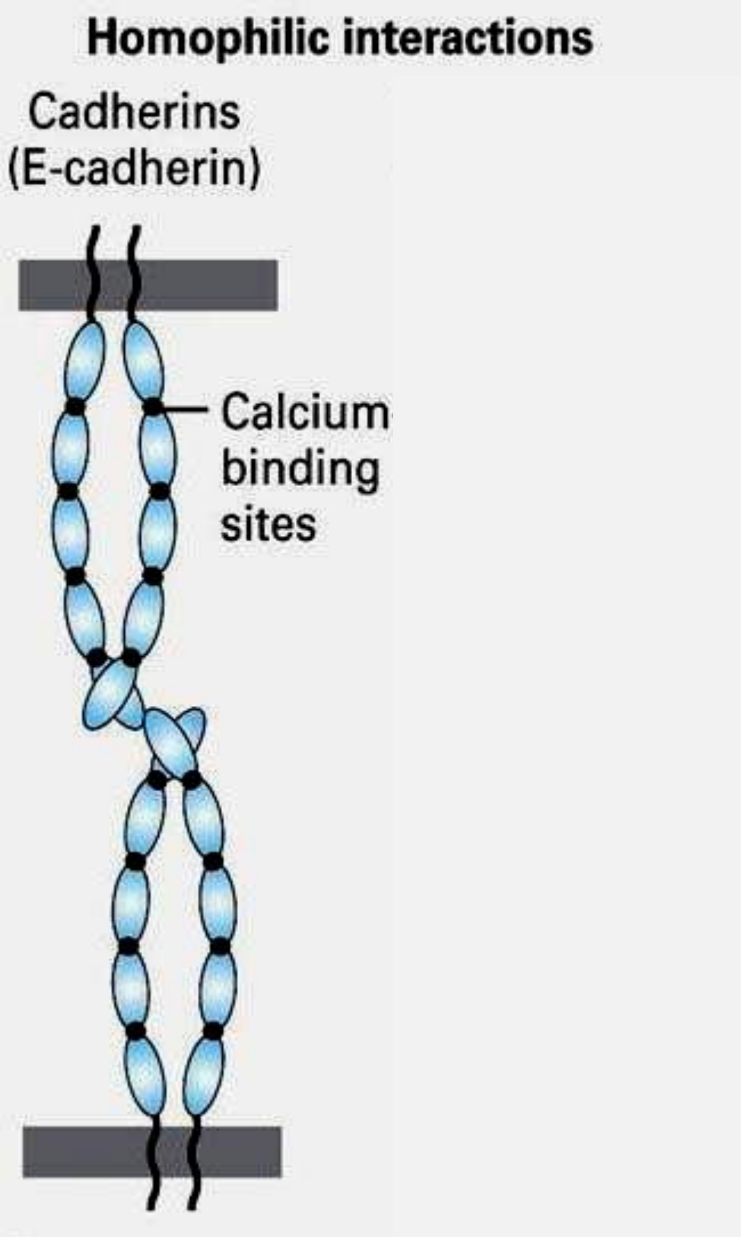

Homophilic interactions
Heterophilic interactions
Cadherins
(E-cadherin)
Ig-superfamily
CAMs (NCAM)
Integrins
(αvβ3)
Selectins
(P-selectin)
Calcium-
binding
sites
α
β
Fibronectin
Sugars
Glycoprotein
Cadherin domain
Ig domain
Type III fibronectin repeat
Lectin domain

CAMs and adhesion receptors

Four major families

1) Dimeric E-cadherins

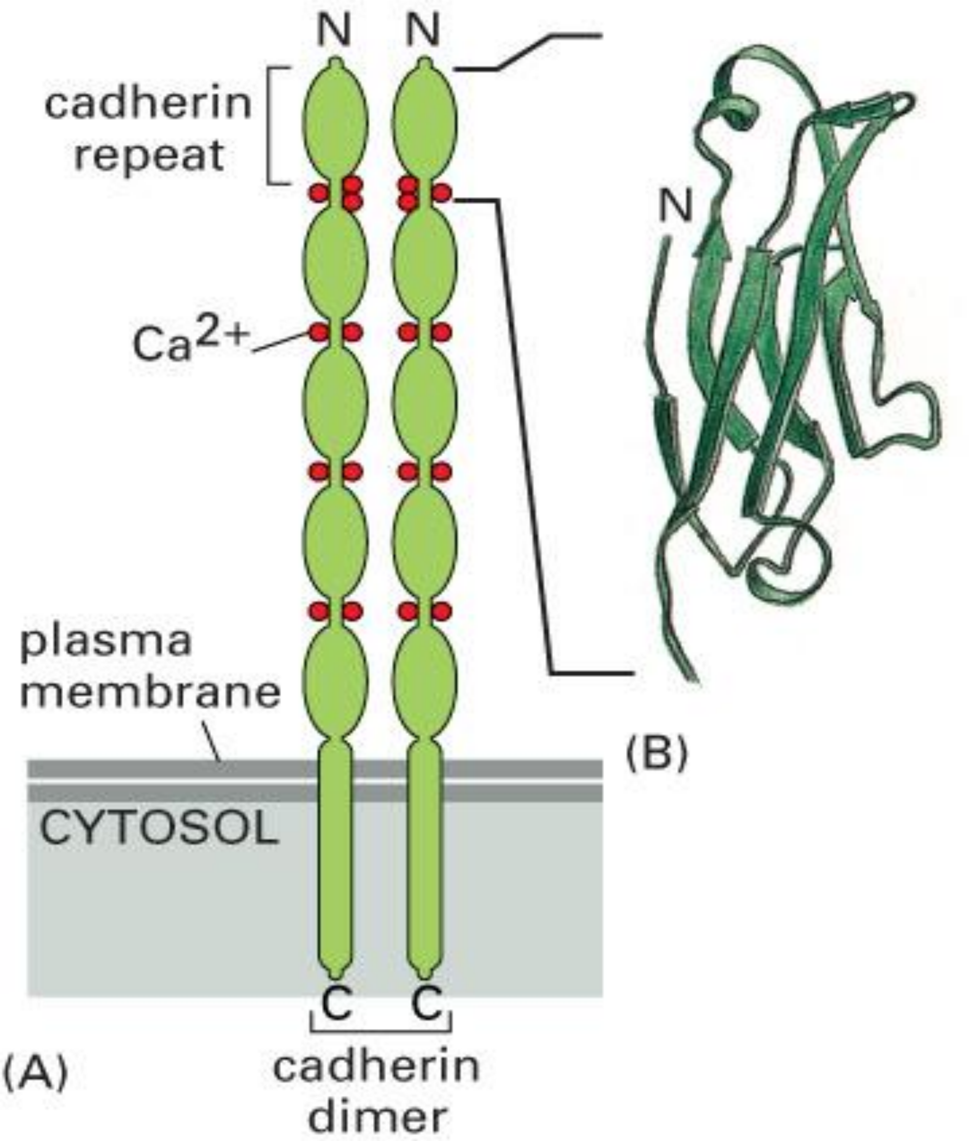
- Homophilic (self) cross-bridges with E-cadherins
- Each major type of cell in the body has a different type of cadherin
- Each type of cadherin can bind to *only cadherin's of the same type*



Cadherins

- Cadherins: Large family of cell surface proteins that mediate homophilic Ca++ dependent cell-cell adhesion.
- The classical cadherins, e.g. E-,N-, P-, L-cadherins occur in the epithelial, neuronal placental and liver tissues respectively.

700-750 a.a glycoprotein
Five fold external parts
Four with Ca++



Cell-cell Adhesion
Regulation of cadherins

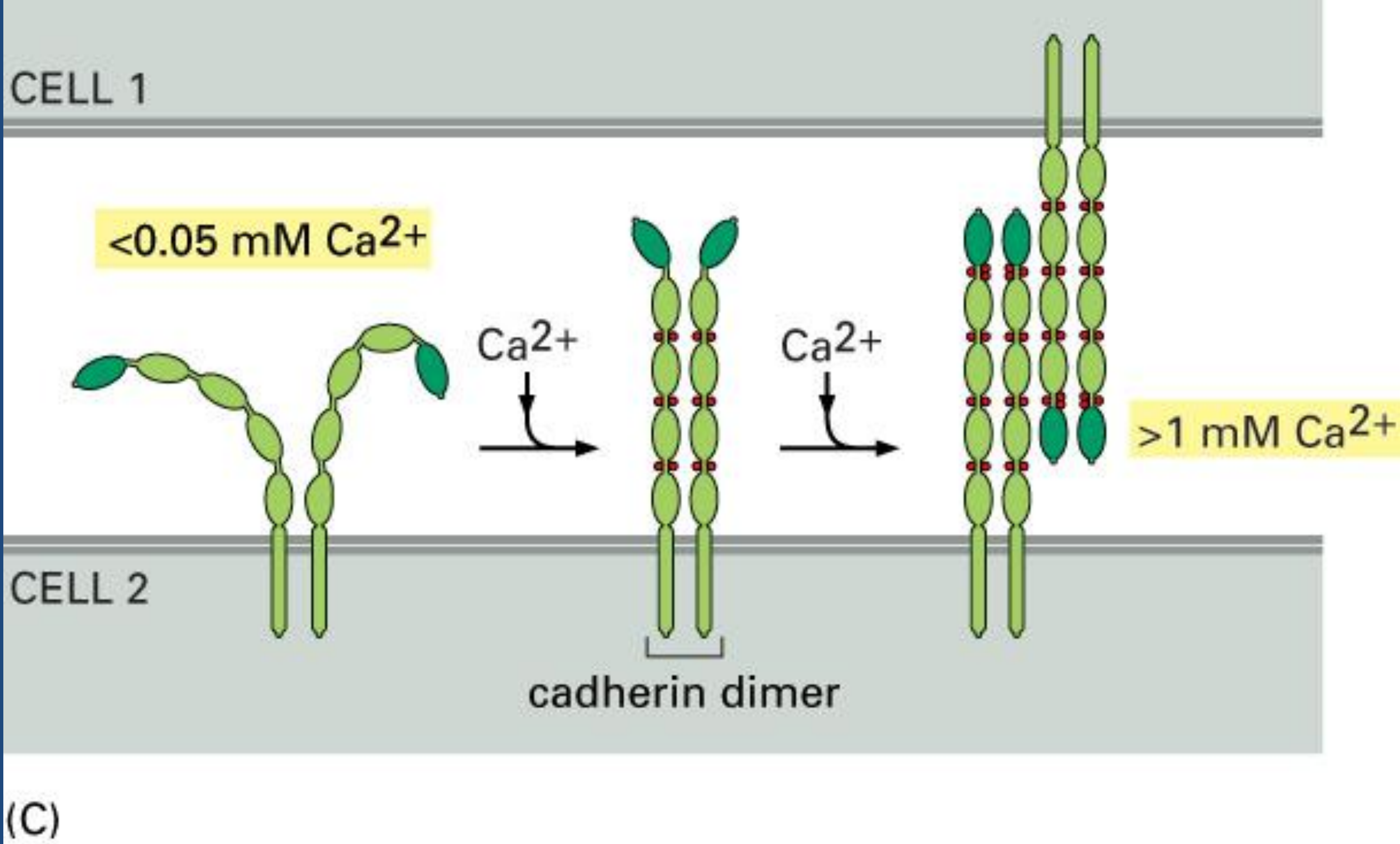
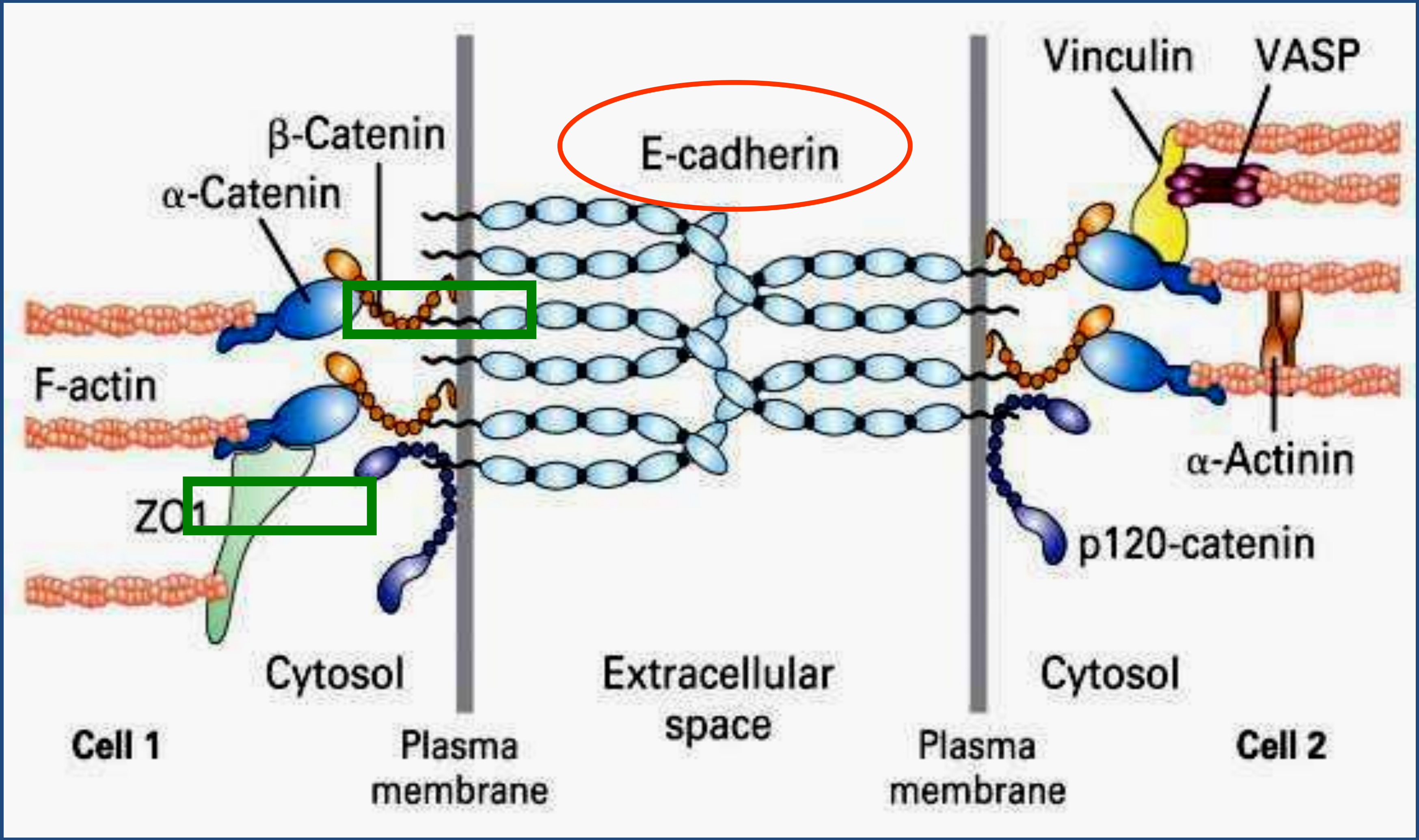


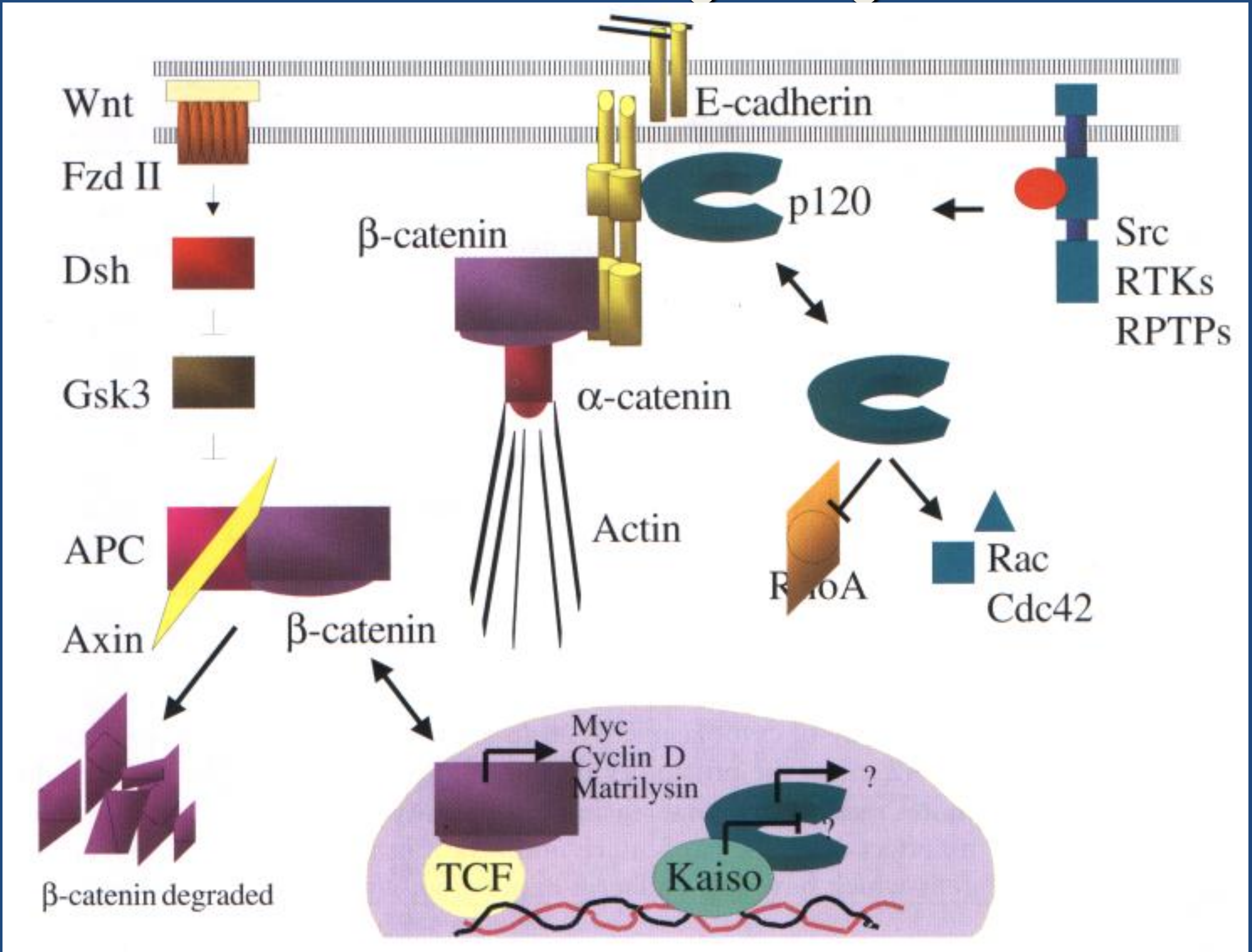
Figure 19–24 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

Cytosolic domains bind to multiple adapter proteins

- connect the junctions to actin filaments (F-actin)
- participate in **signaling pathways** (e.g., β-catenin).



Cadherin signaling

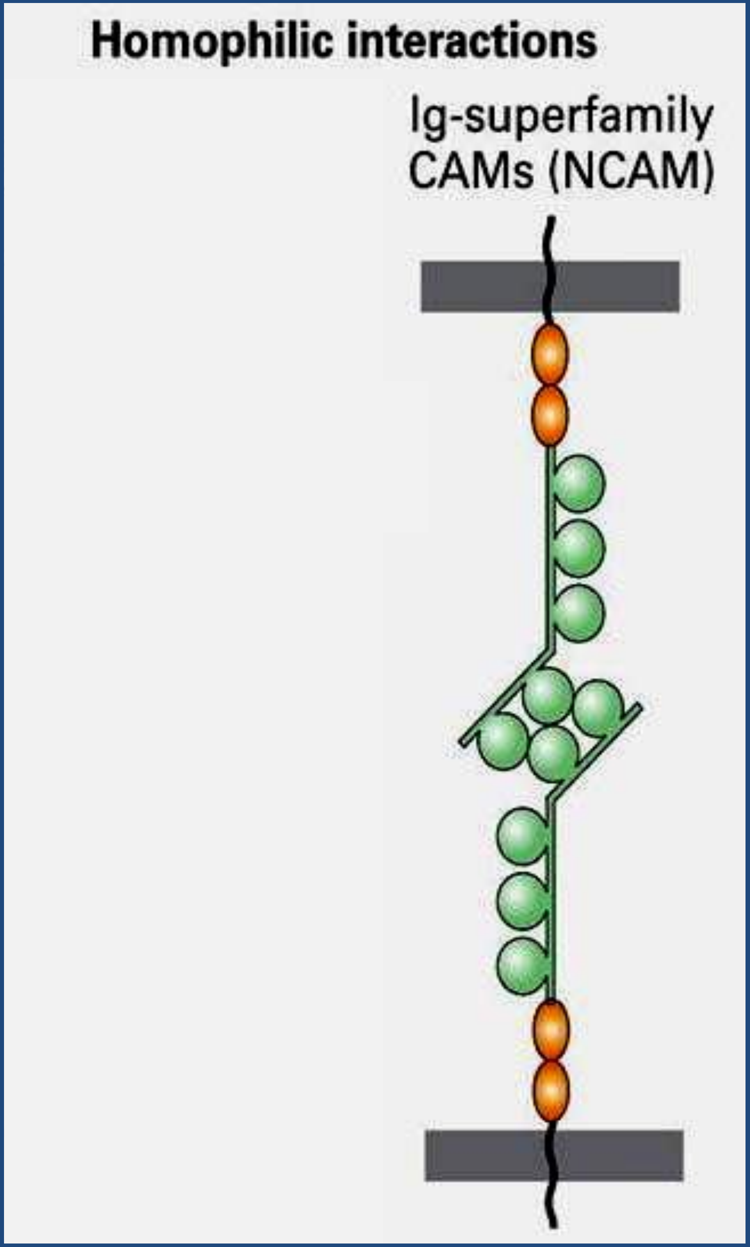


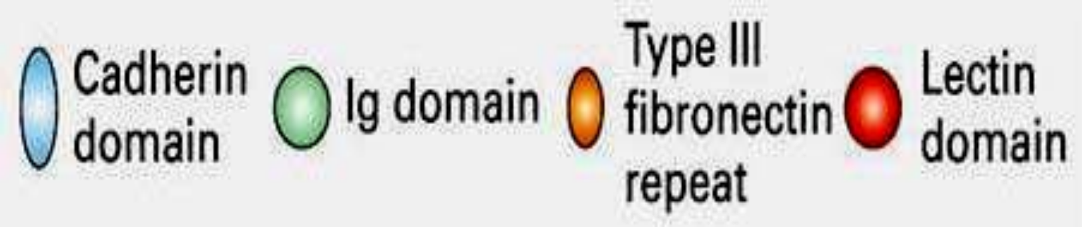
CAMs and adhesion receptors

Four major families

2) Members of the immunoglobulin (Ig) family

- Homophilic linkages and heterophilic (nonself) linkages





Ca++ independent cell-cell adhesion molecule

Ig-superfamily of adhesion molecules:

- includes around 70 members.
- All posses one or more Ig-like domain.
- Ig-like domains are - β sheets proteins stabilized by disulphide bond.
- Ig domains are resistant to proteases

Neural cell adhesion molecule (N-CAM), intercellular adhesion molecule (ICAM)

Calcium-independent

Immunoglobulin (Ig) superfamily

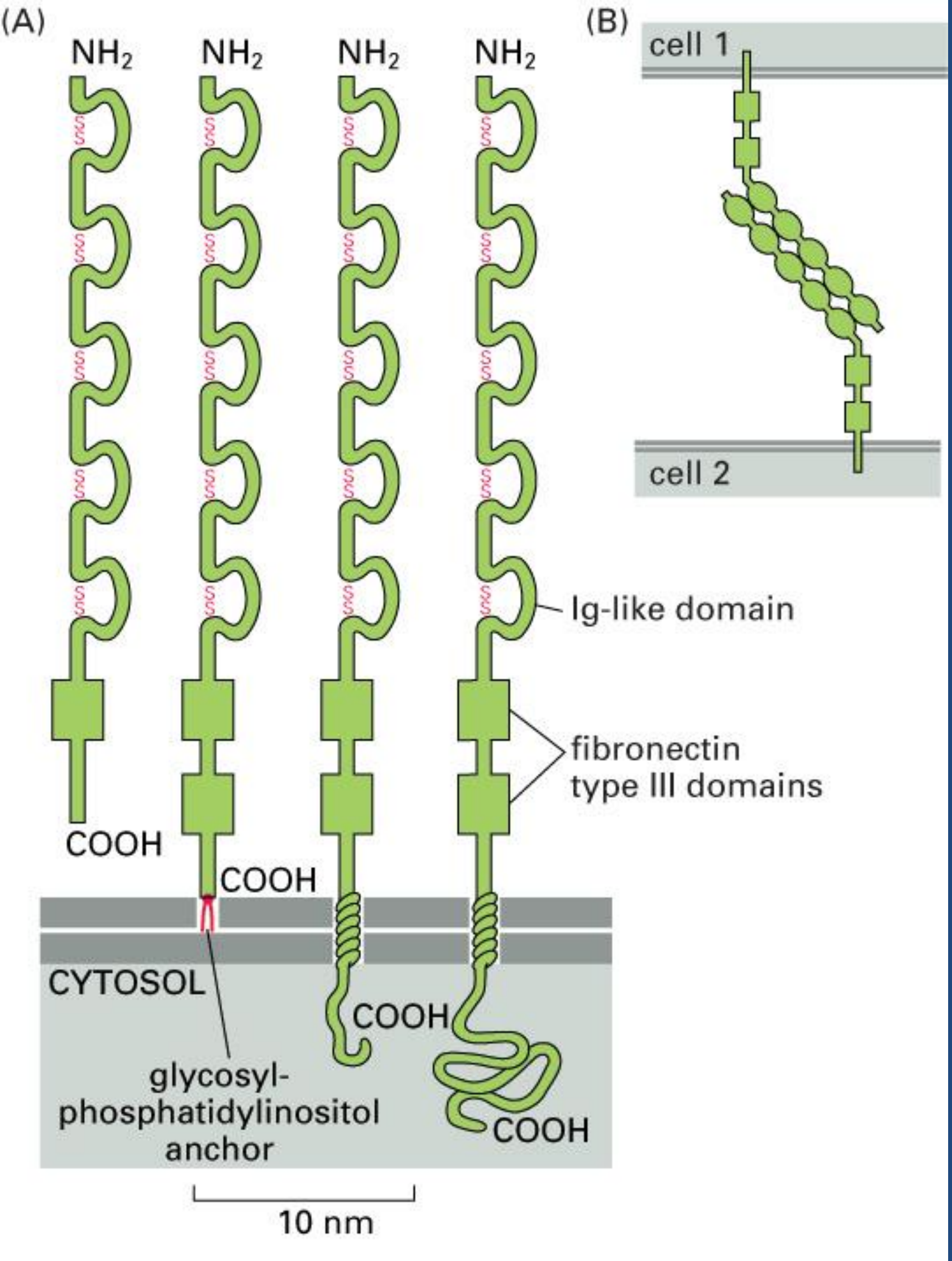
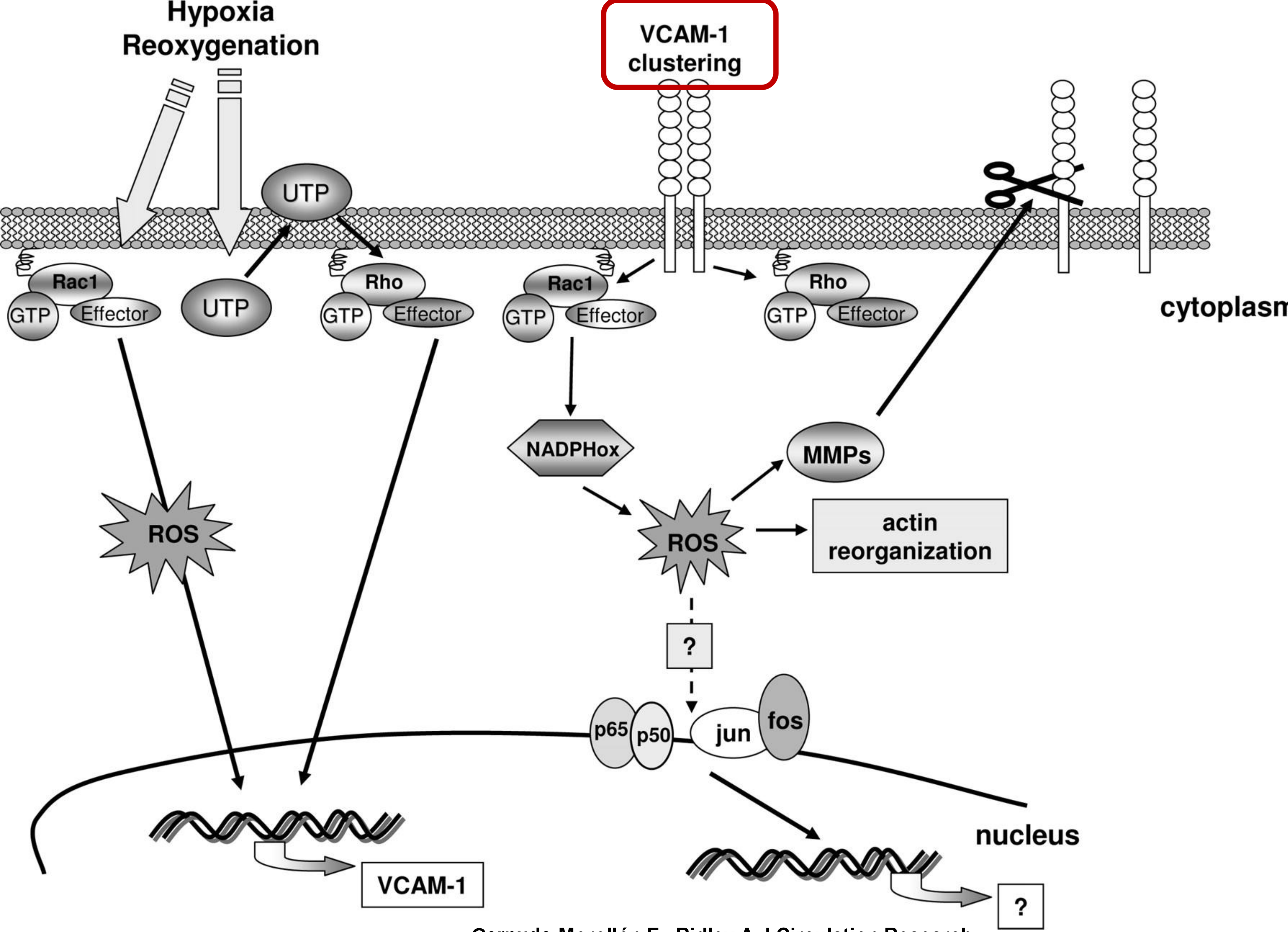


Figure 19–31. Molecular Biology of the Cell, 4th Edition.



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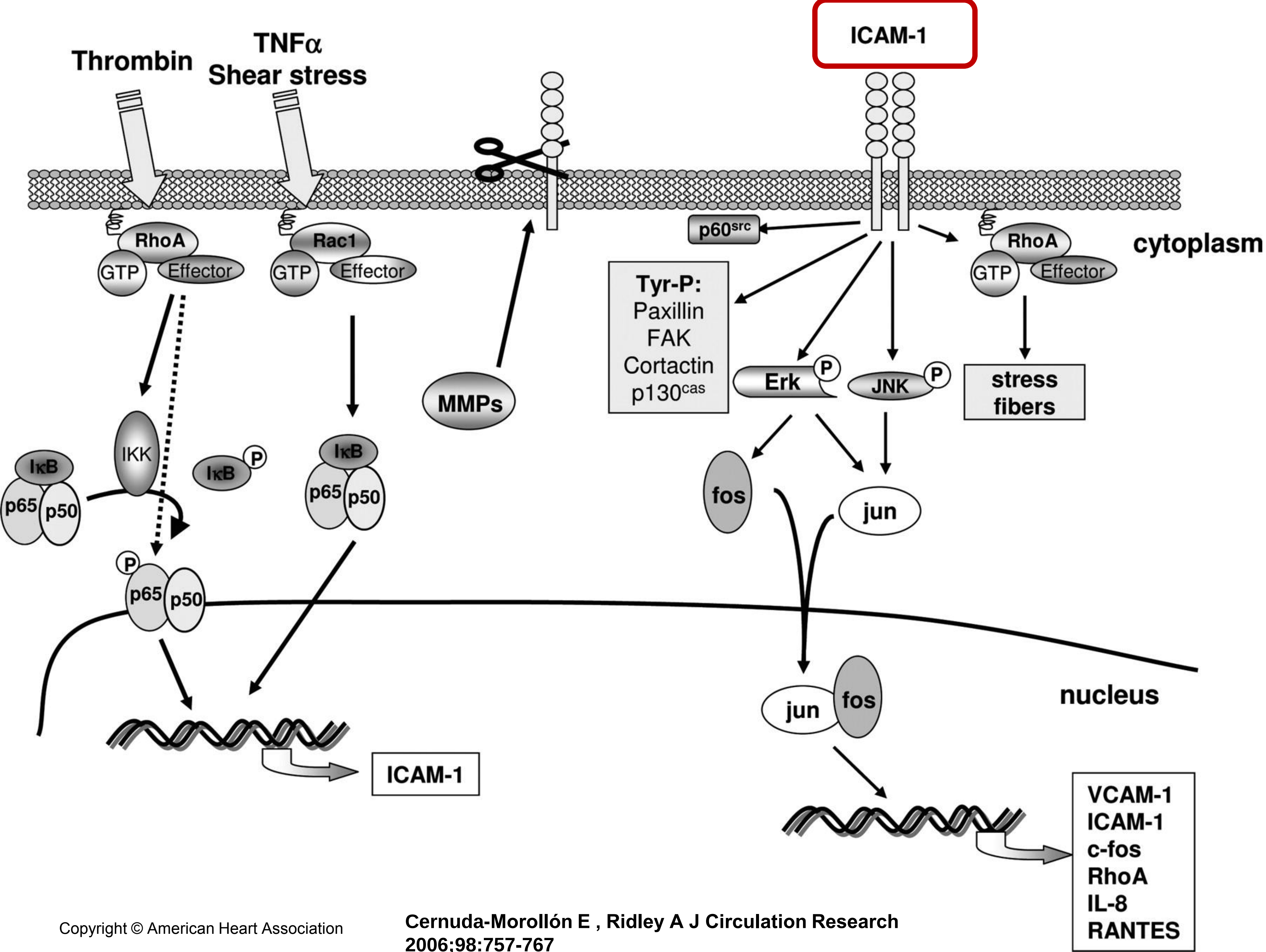
Cernuda-Morollón E , Ridley A J Circulation Research 2006;98:757-767



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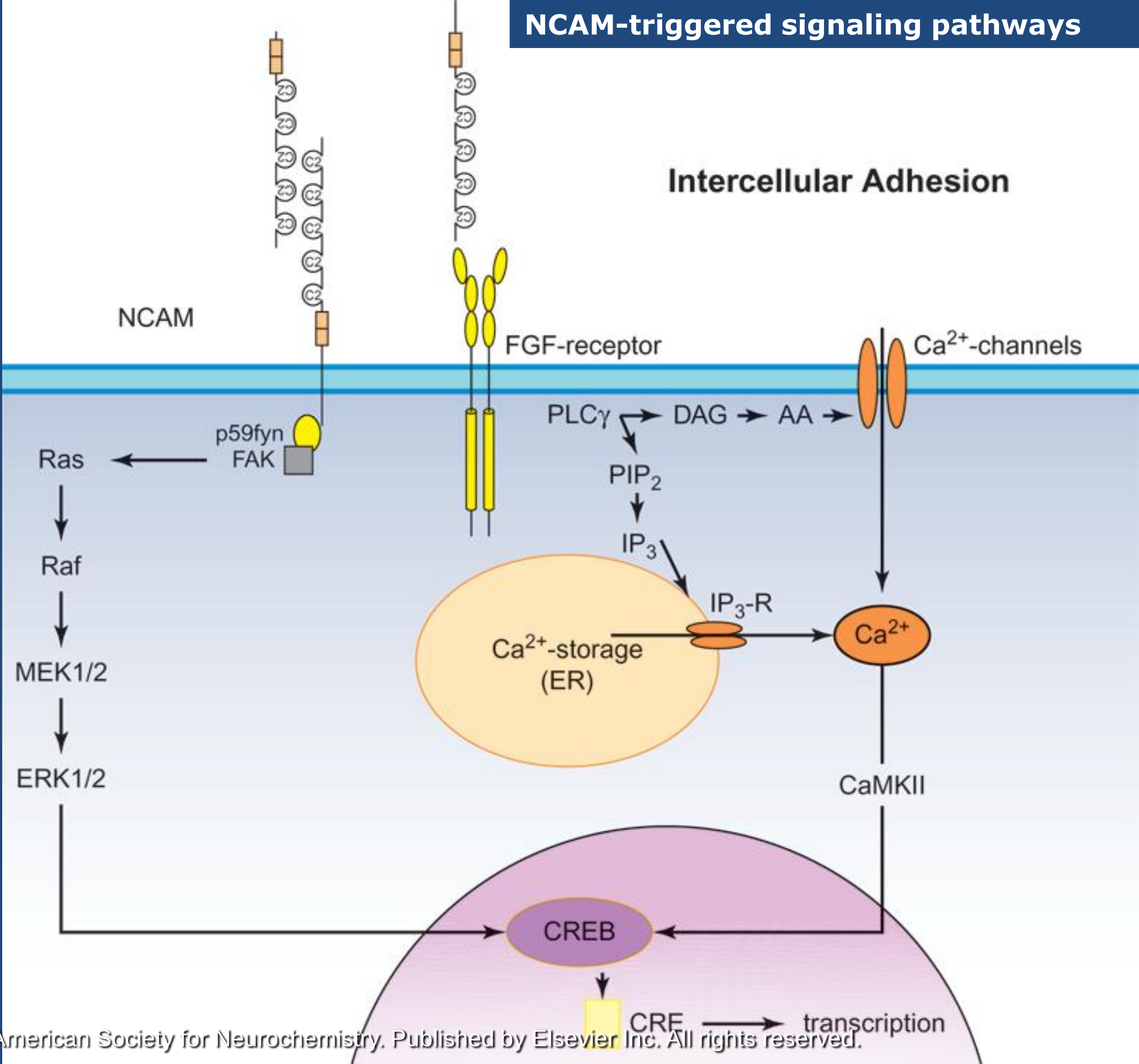
Cernuda-Morollón E , Ridley A J Circulation Research 2006;98:757-767

NCAM-triggered signaling pathways



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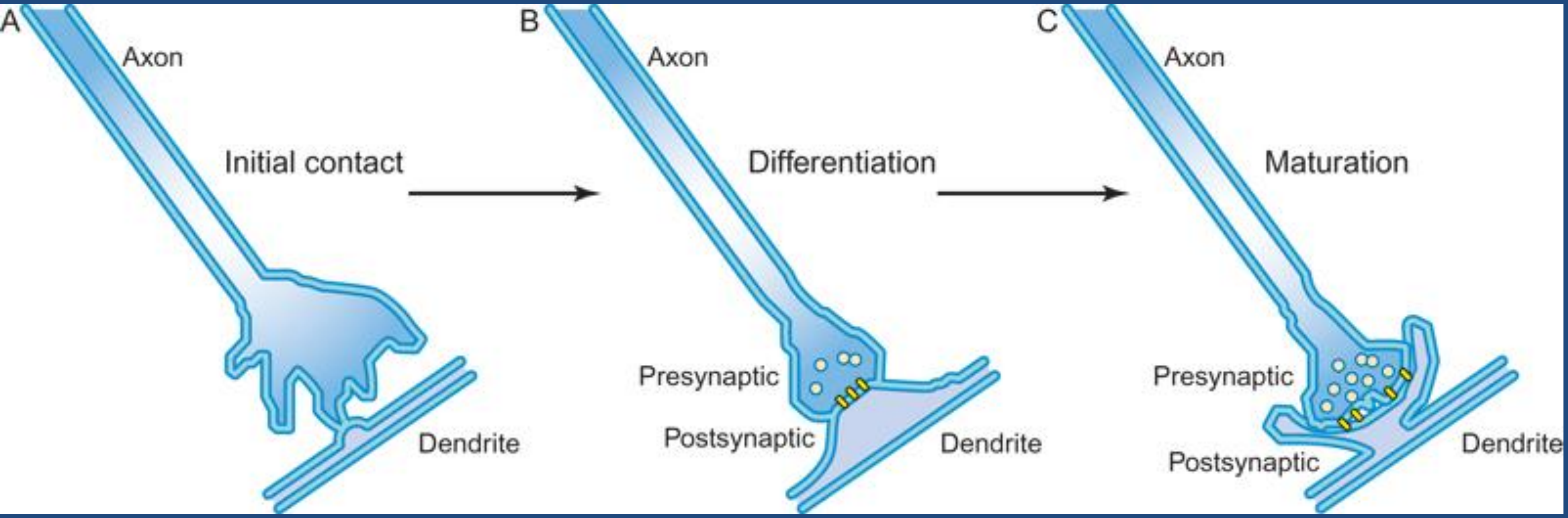

CNS synapse formation: a multi-step process.

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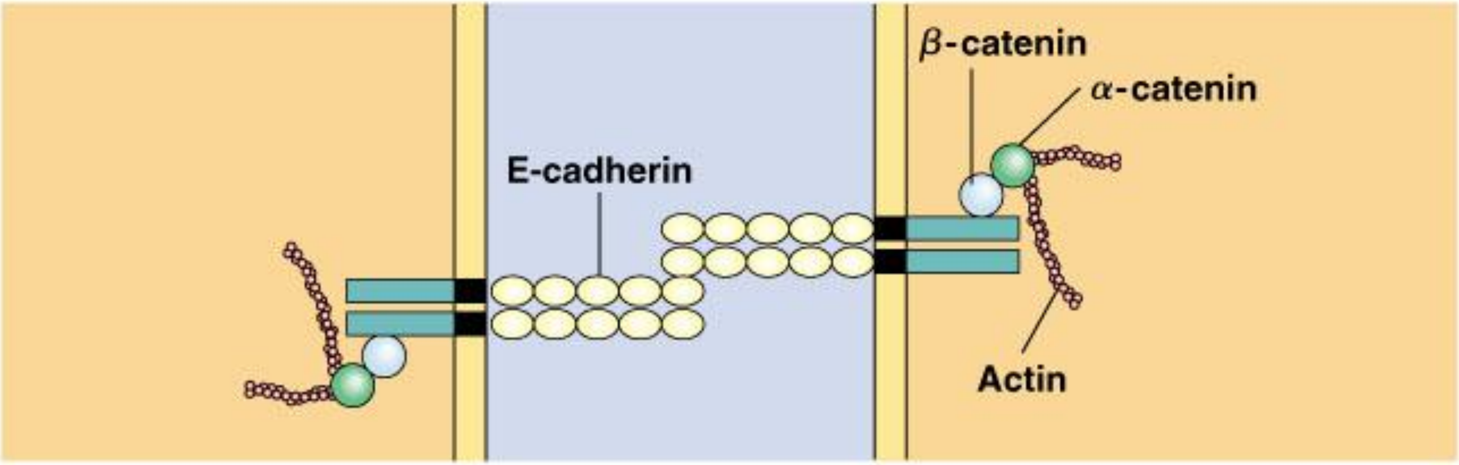
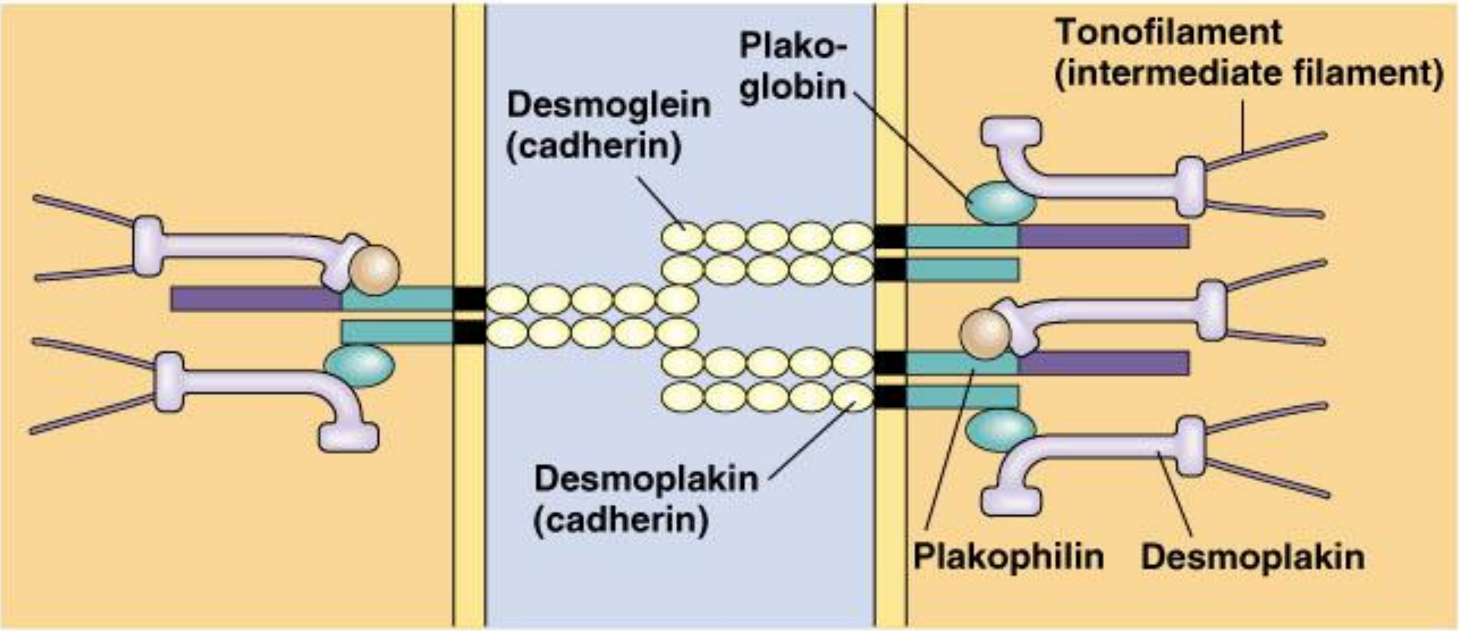


(a) Adherens junction



(b) Desmosome

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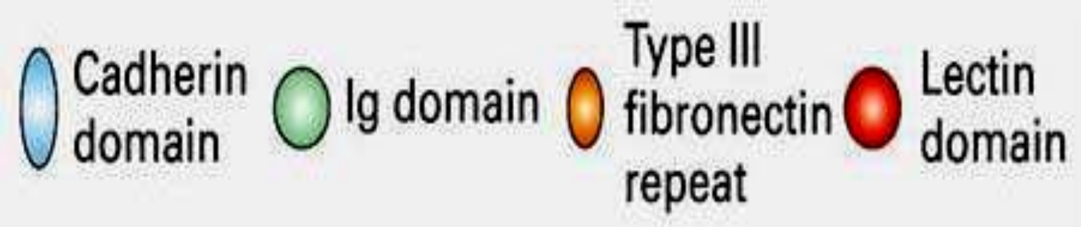
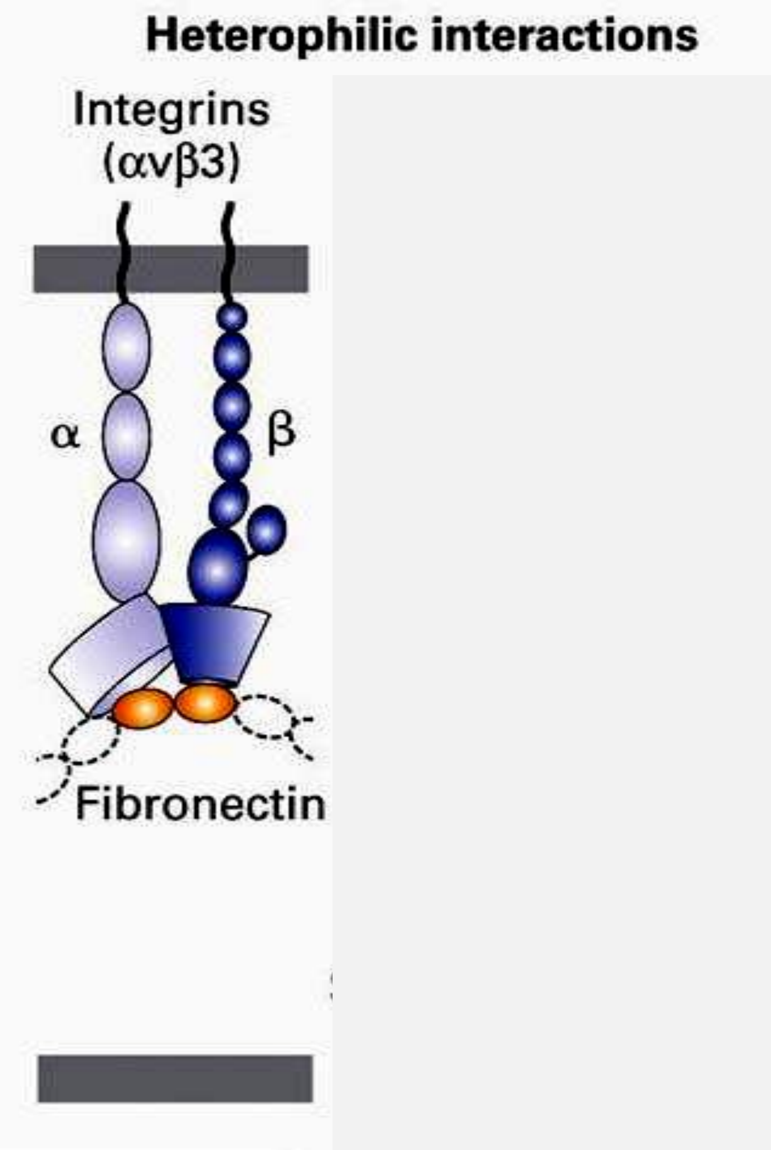
3) Heterodimeric integrins

- bind to multiadhesive matrix proteins (eg. Fibronectin)
  - ◆ function as CAMs or as adhesion receptors





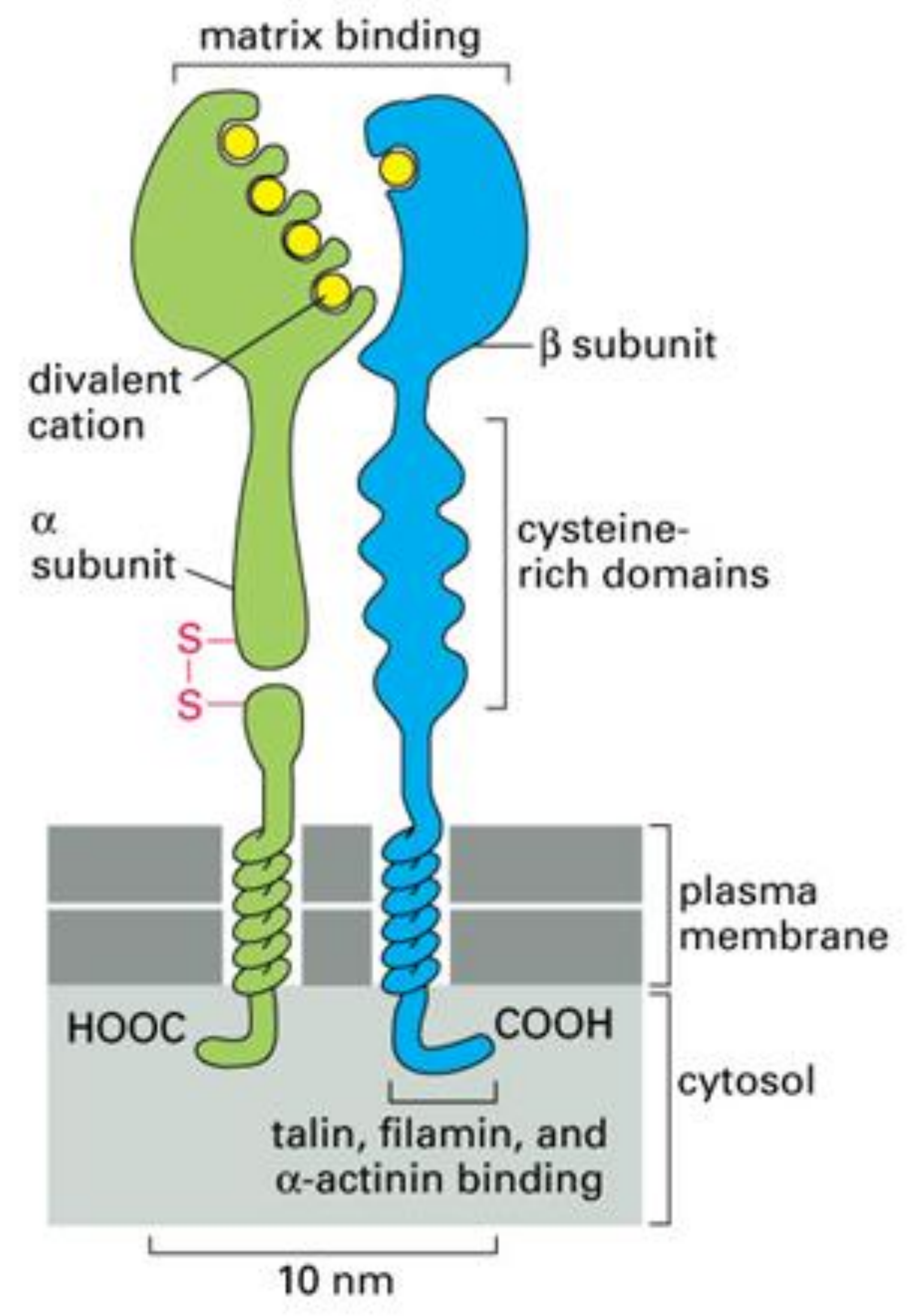
Integrins: A Family of Cell Surface Receptors for ECM Proteins

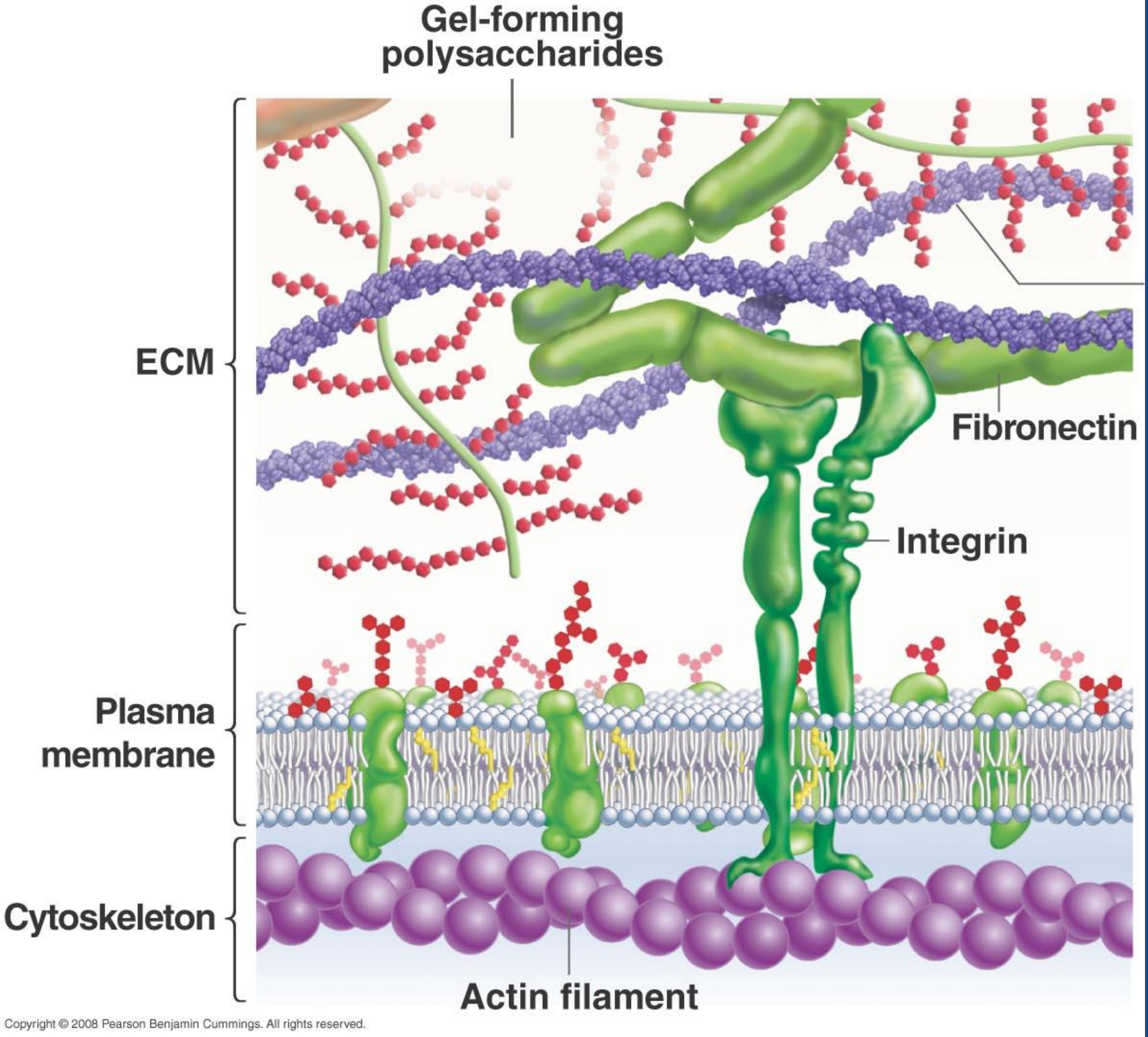
Always heterodimers

Alpha subunits contain divalent cation binding sites

Beta subunits have extracellular disulfide bonds. Binds talin, actinin

Binding is Ca dependent
May involve actin filaments but not associated with cells junctions





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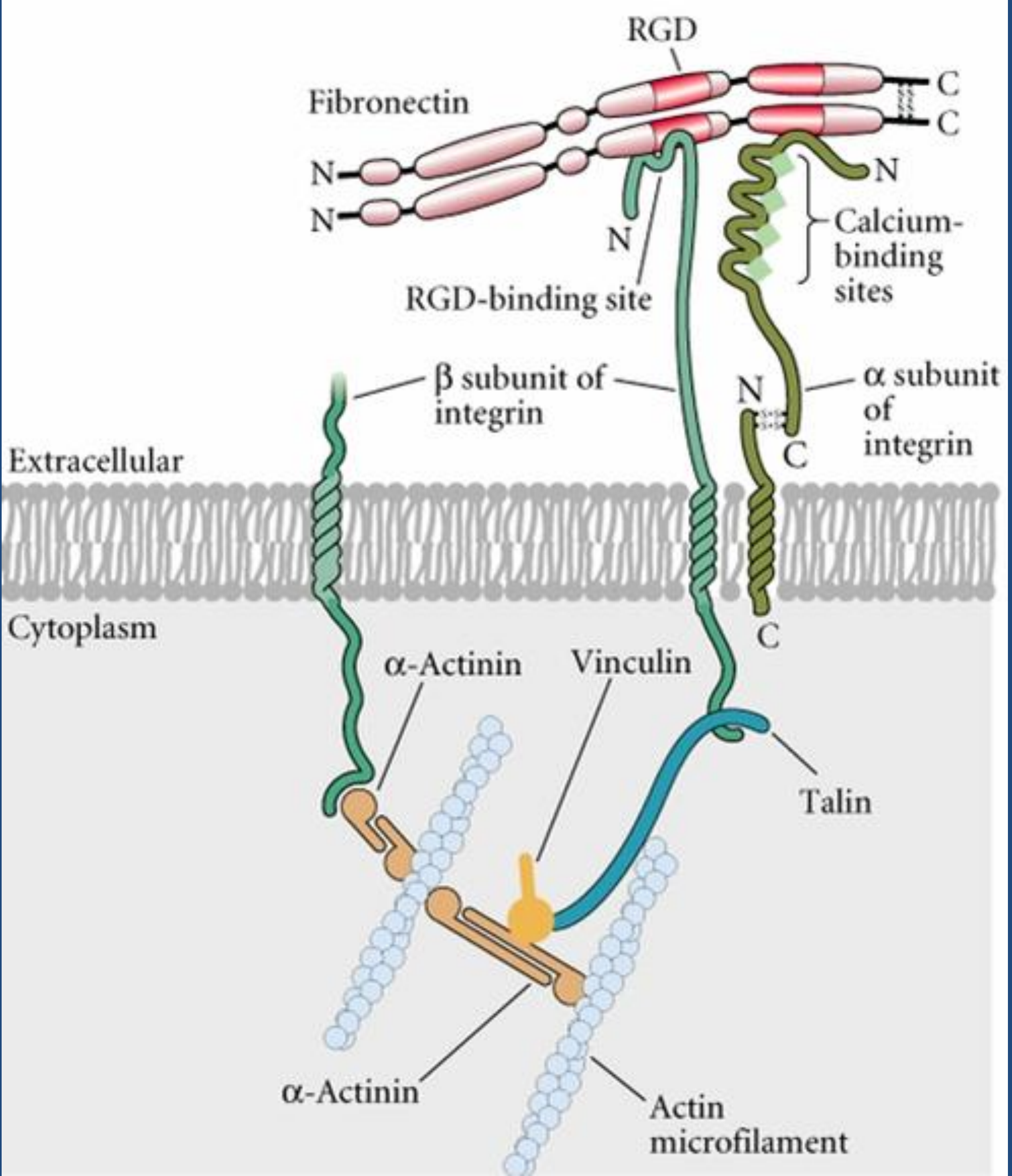
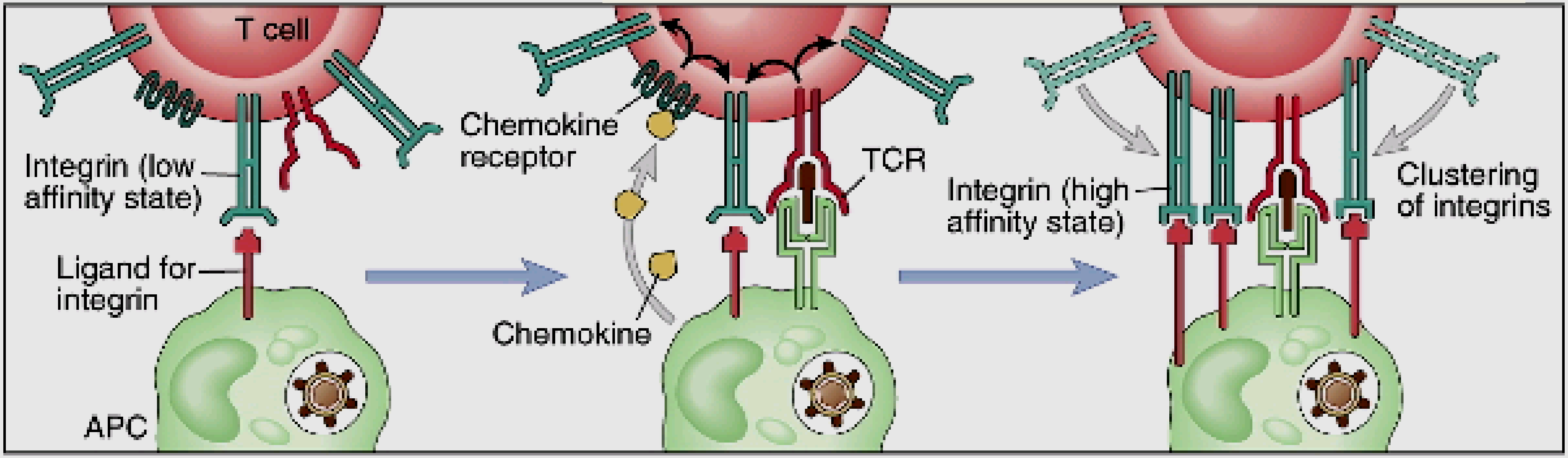
INTEGRINS

Important roles:

- platelet aggregation,
- inflammation,
- immune function,
- wound healing,
- tumor metastasis,
- tissue migration during embryogenesis.
- signalling pathways, transmitting signals both into and out from cells

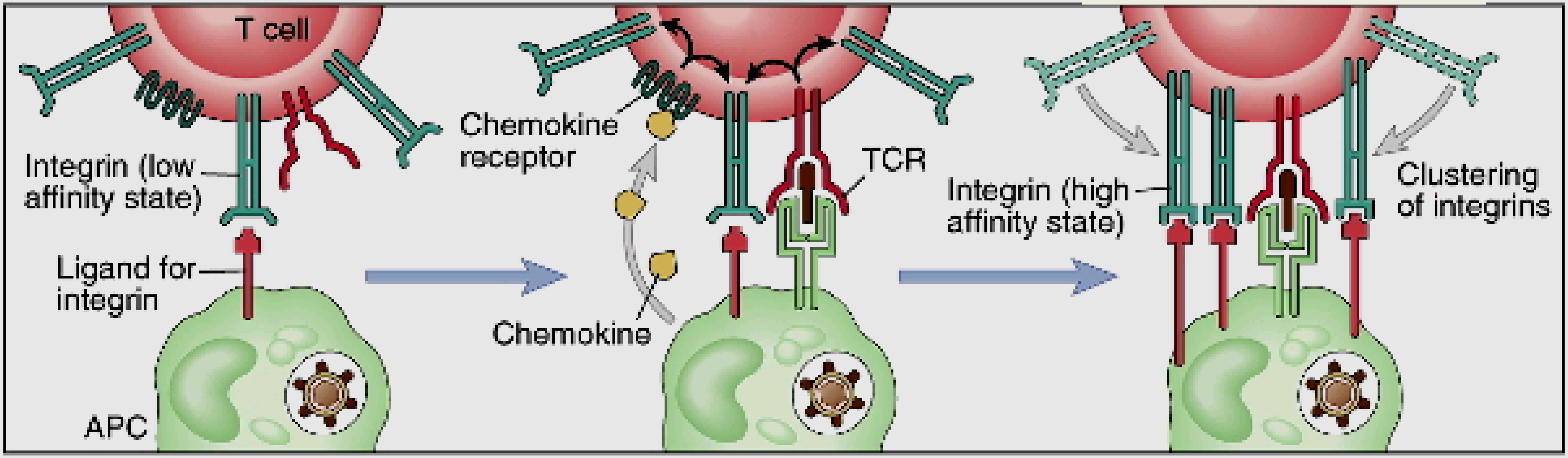
Focal Adhesion Complex





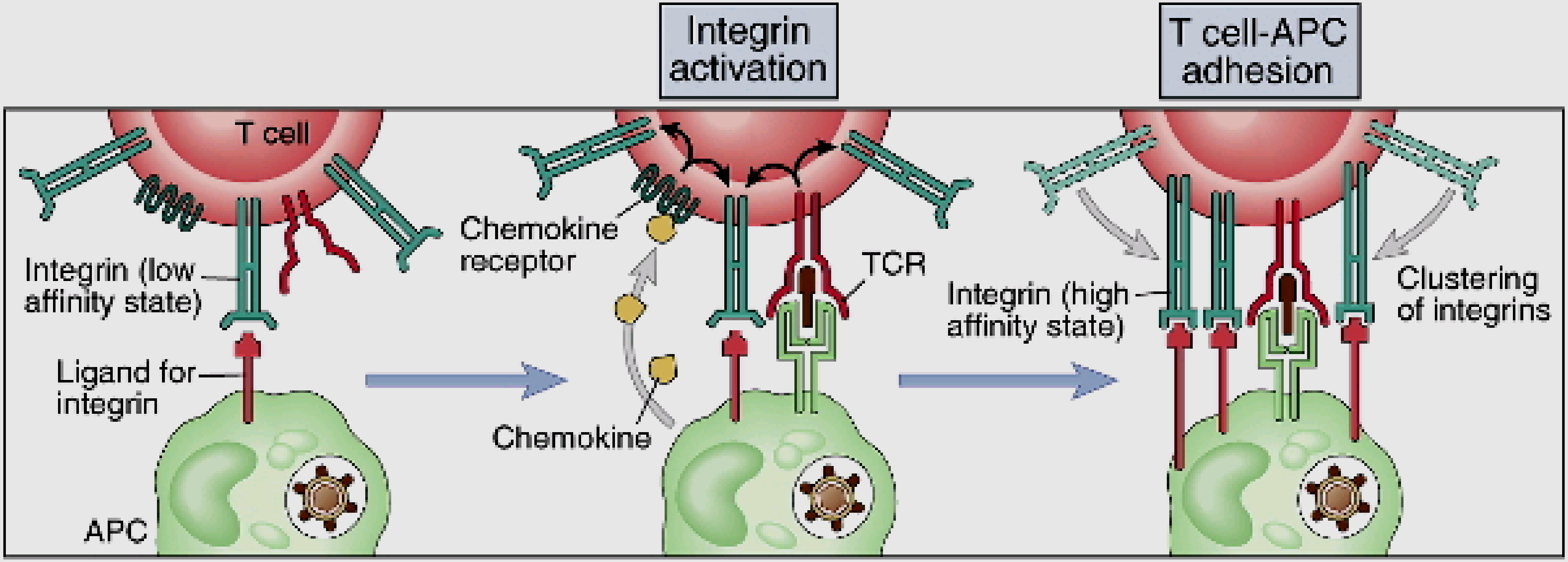
Weak adhesion ⇒ no T cell response

Integrin activation



Weak adhesion ⇒ no T cell response

Signals delivered by chemokines and antigen recognition act on integrins



Integrin activation

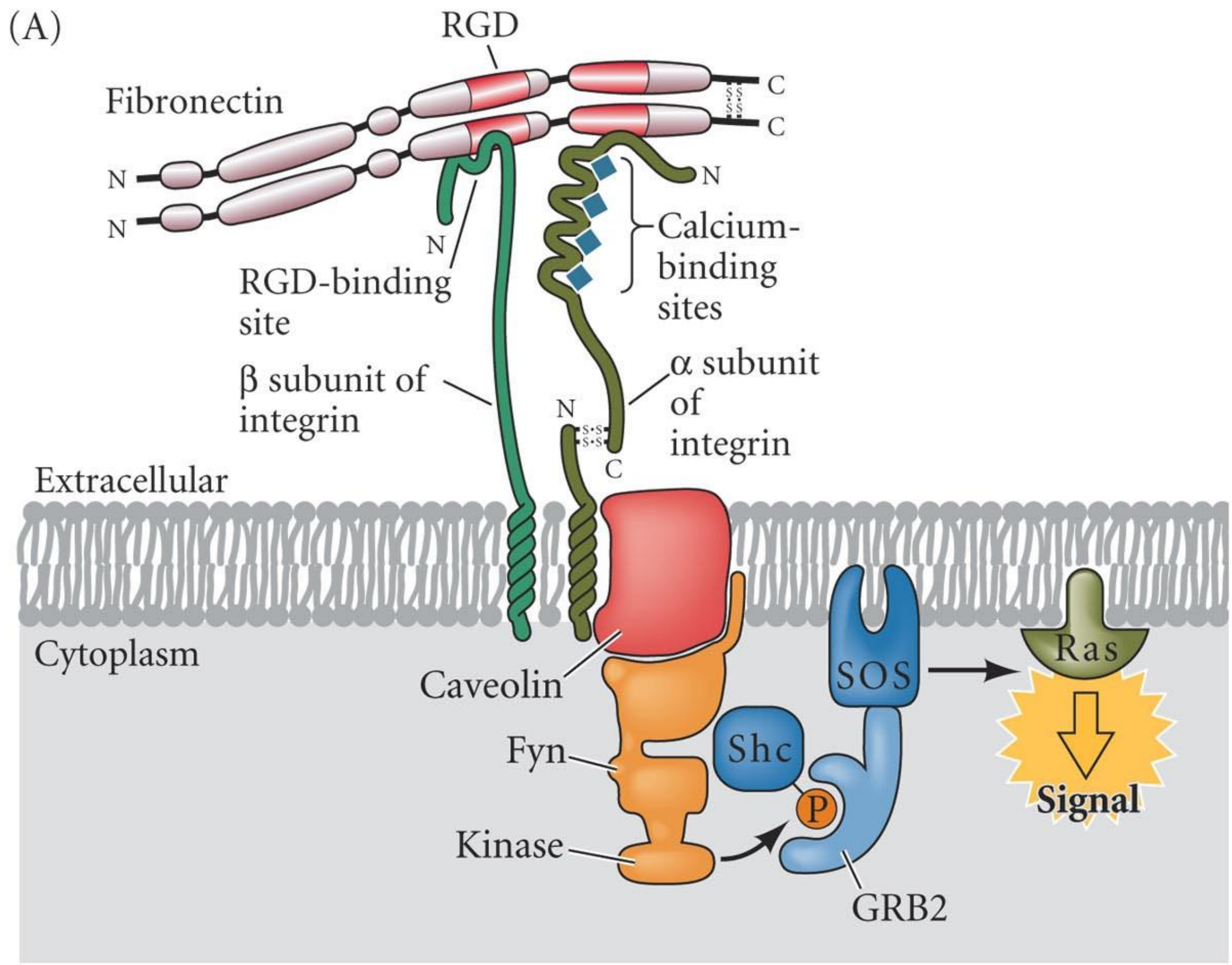
T cell-APC adhesion

Weak adhesion ⇒ no T cell response

Signals delivered by chemokines and antigen recognition act on integrins

Clustering and increase in affinity of integrins ⇒ strong T cell-APC adhesion ⇒ T cell response

Signaling Through Focal Adhesion Molecules



DEVELOPMENTAL BIOLOGY, Seventh Edition, **Figure 6.37 (Part 1)** Sinauer Associates, Inc.

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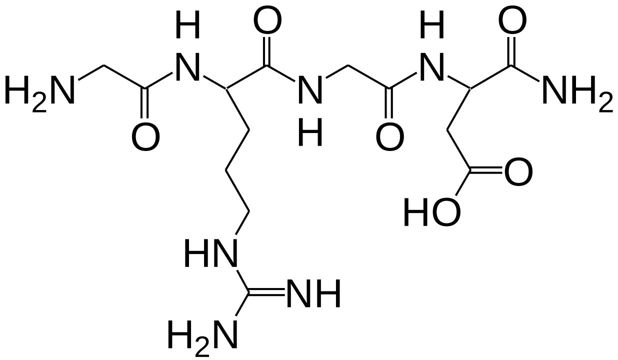
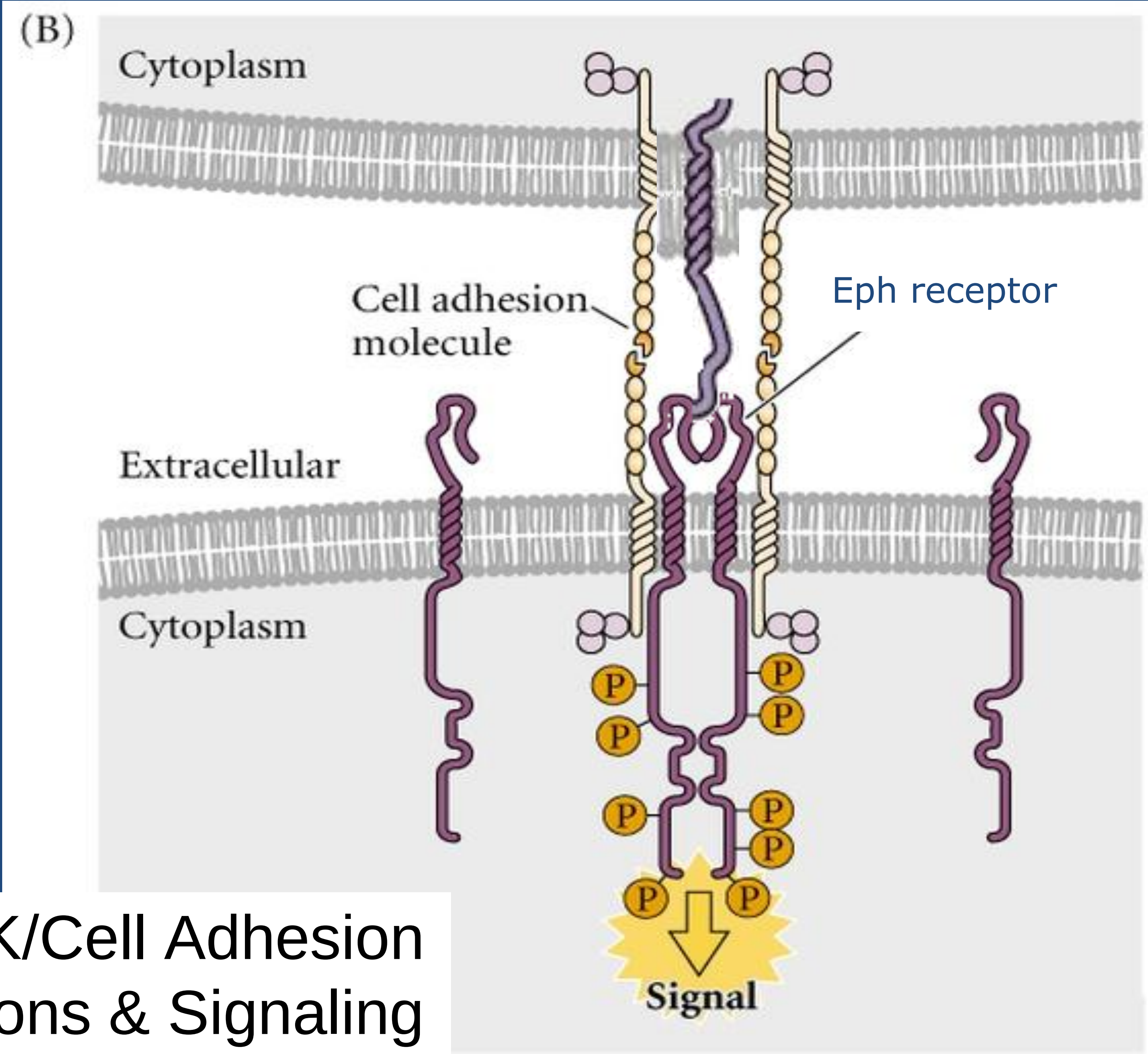
RGD-Promotes Cell Adhesion



Gly-Arg-Gly-Asp

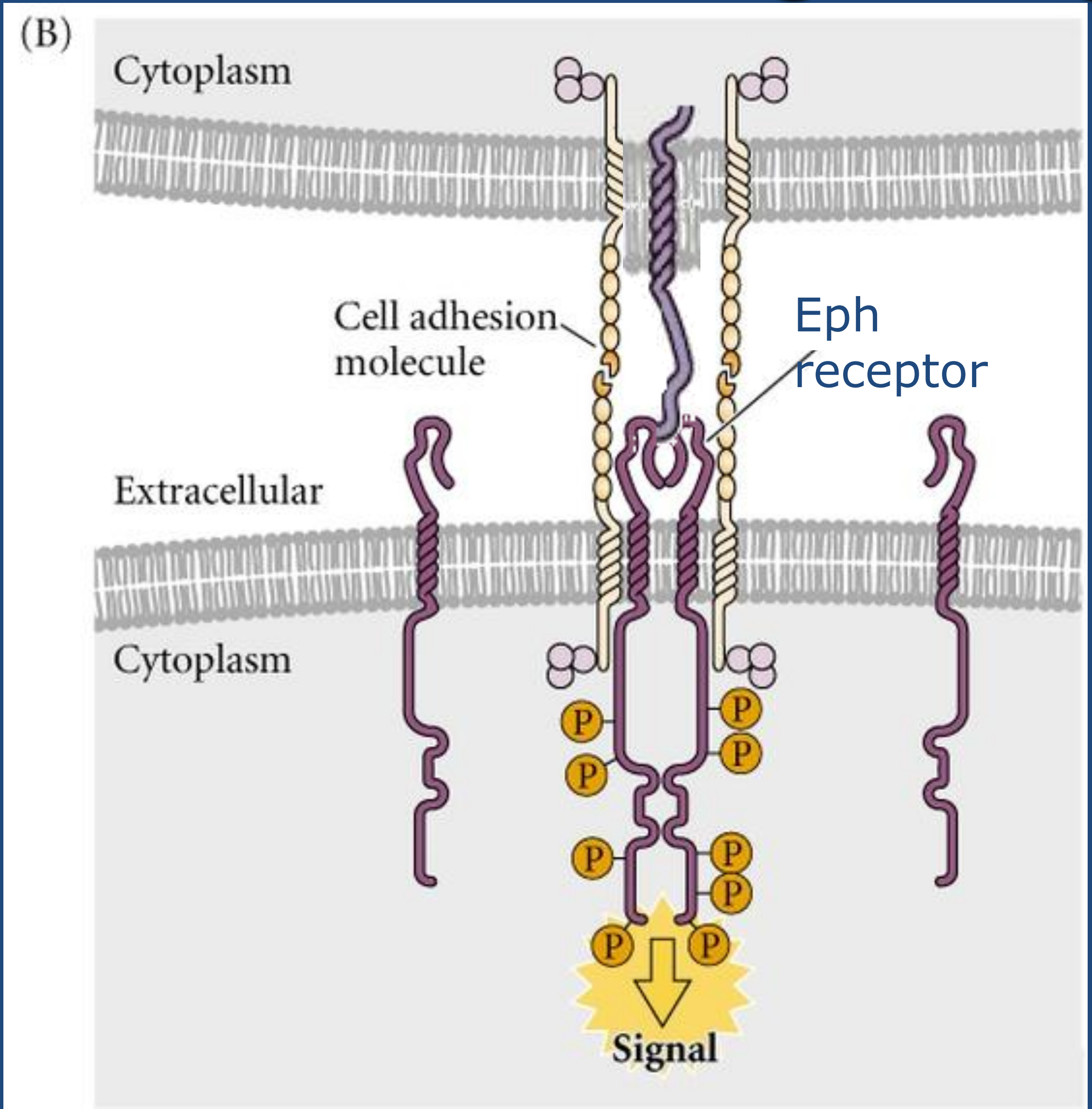
GRGD

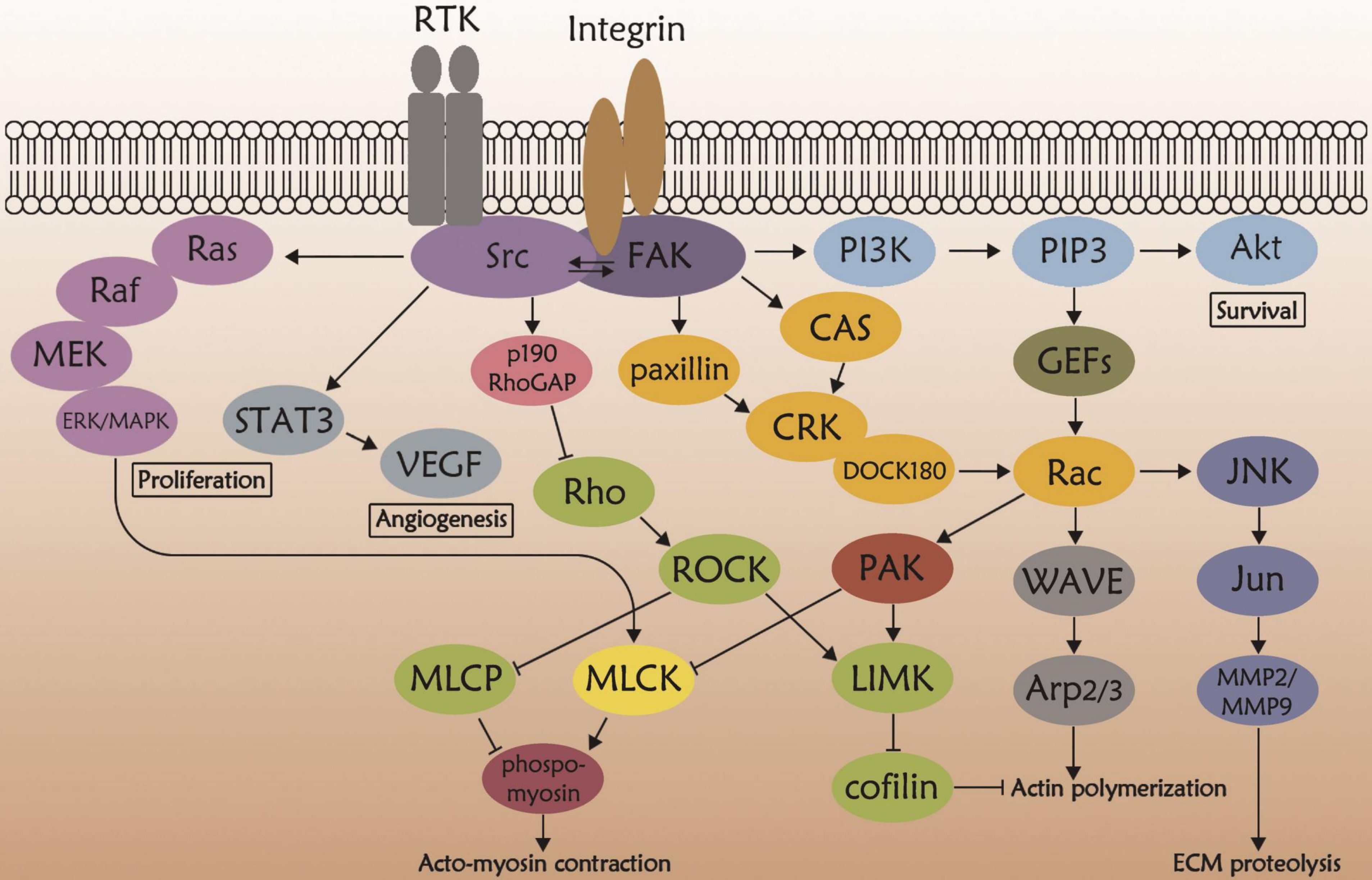
- Soluble peptide inhibits cell adhesion to fibronectin
- Surfaces coated with RGD peptide promote cell attachment and spreading
  - Utilized in numerous biomaterials



Eph RTK/Cell Adhesion Interactions & Signaling

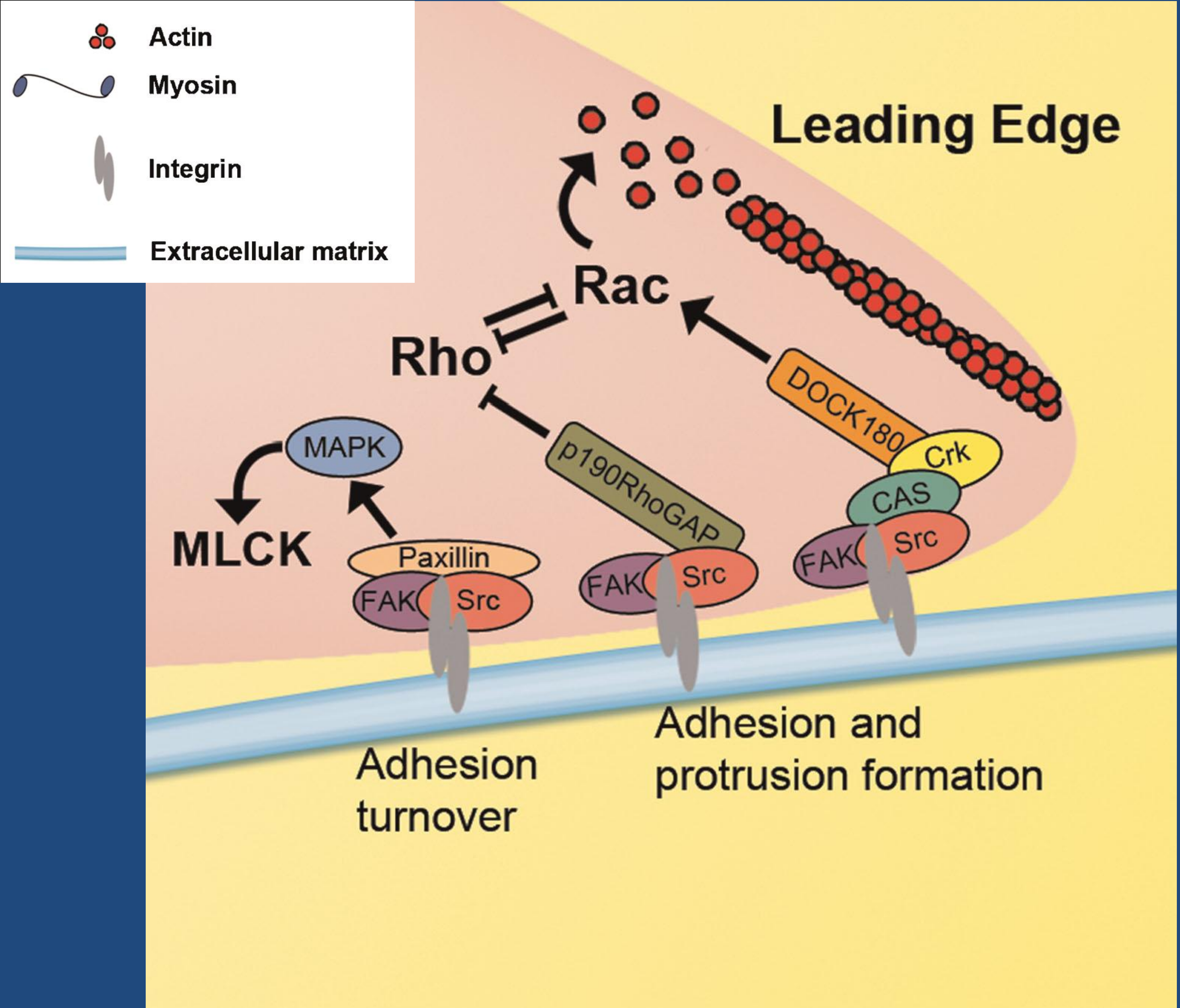
Eph RTK/Cell Adhesion Interactions & Signaling





MIGRATION and INVASION

Guarino (2010)

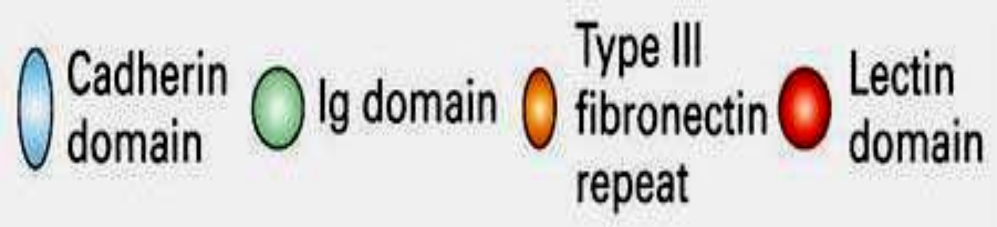

Actin
Myosin
Integrin
Extracellular matrix
Leading Edge
Rac
Rho
DOCK180
Crk
CAS
Src
FAK
p190RhoGAP
Src
FAK
MAPK
MLCK
Paxillin
FAK
Src
Adhesion turnover
Adhesion and protrusion formation

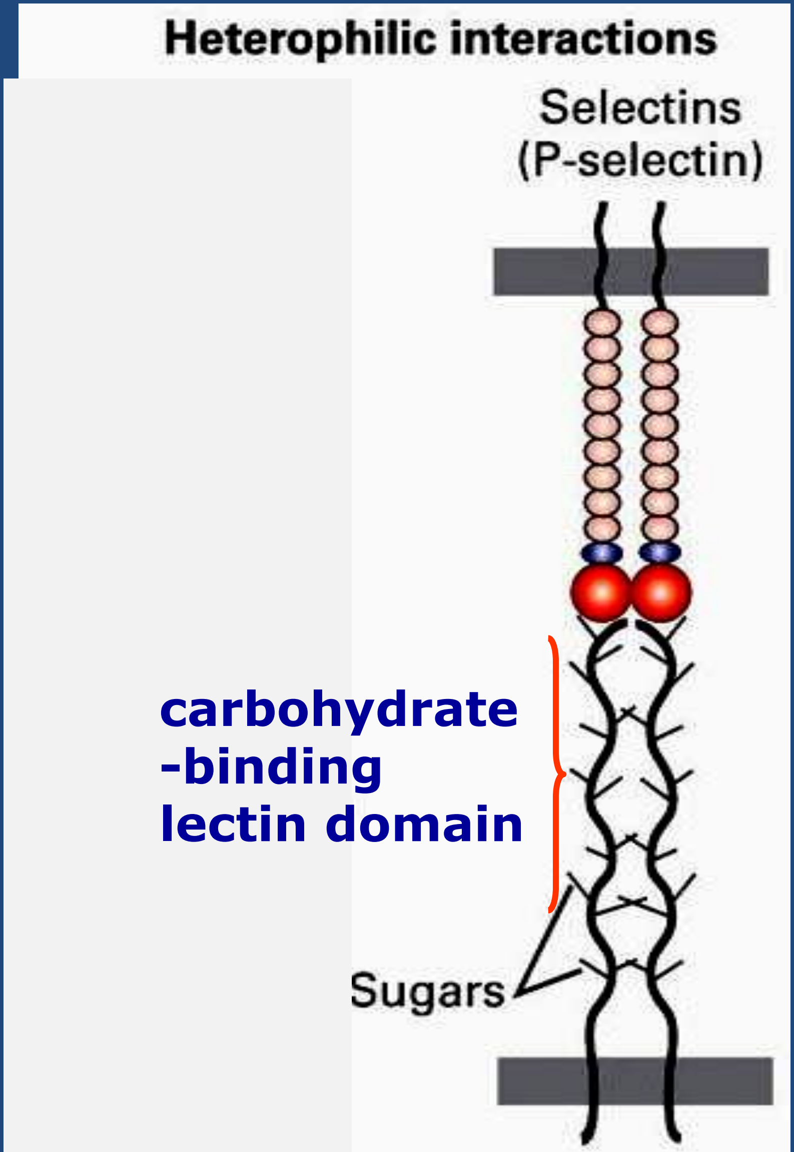
Guarino

◆ 4) Lectins

Lectins bind *weakly and heterotypically* to oligosaccharides of many types through the large extracellular domain.

Selectins are lectins that are expressed in endothelial cells.





Glycoprotein
Or
Glycolipid

SELECTINS

- Surface carbohydrate binding protein.
- Ex. Lectins in the presence of Ca ions *bind to specific oligosaccharides on another cell (recognition!)*
- All are structurally closely related having, at their N-terminal **a carbohydrate recognition (lectin) domain and variable numbers of repeats related to complement regulatory proteins.**
- Heterophilic cell adhesion bind protein to **another** type on a cell.
- **This binding *is weak untill bind tightly by their integrins*.**

SELECTINS

- Are earliest expressed in inflammatory responses
- Lead to neurtophil activation and extravasation
- L-selectin
- E-selectin
- P-selectin
- Bind to SLe^x of neutrophil

- L-selectin down regulated by IL-1
- P-selectin up-regulated by thrombin, histamine, peroxides, TNF-a, IL-4, IL-1, and IFN-g
- E-selectin up-regulated IL-1b, TNFa and LPS

Selectin-mediated cell-cell adhesion (blood cell rolling)

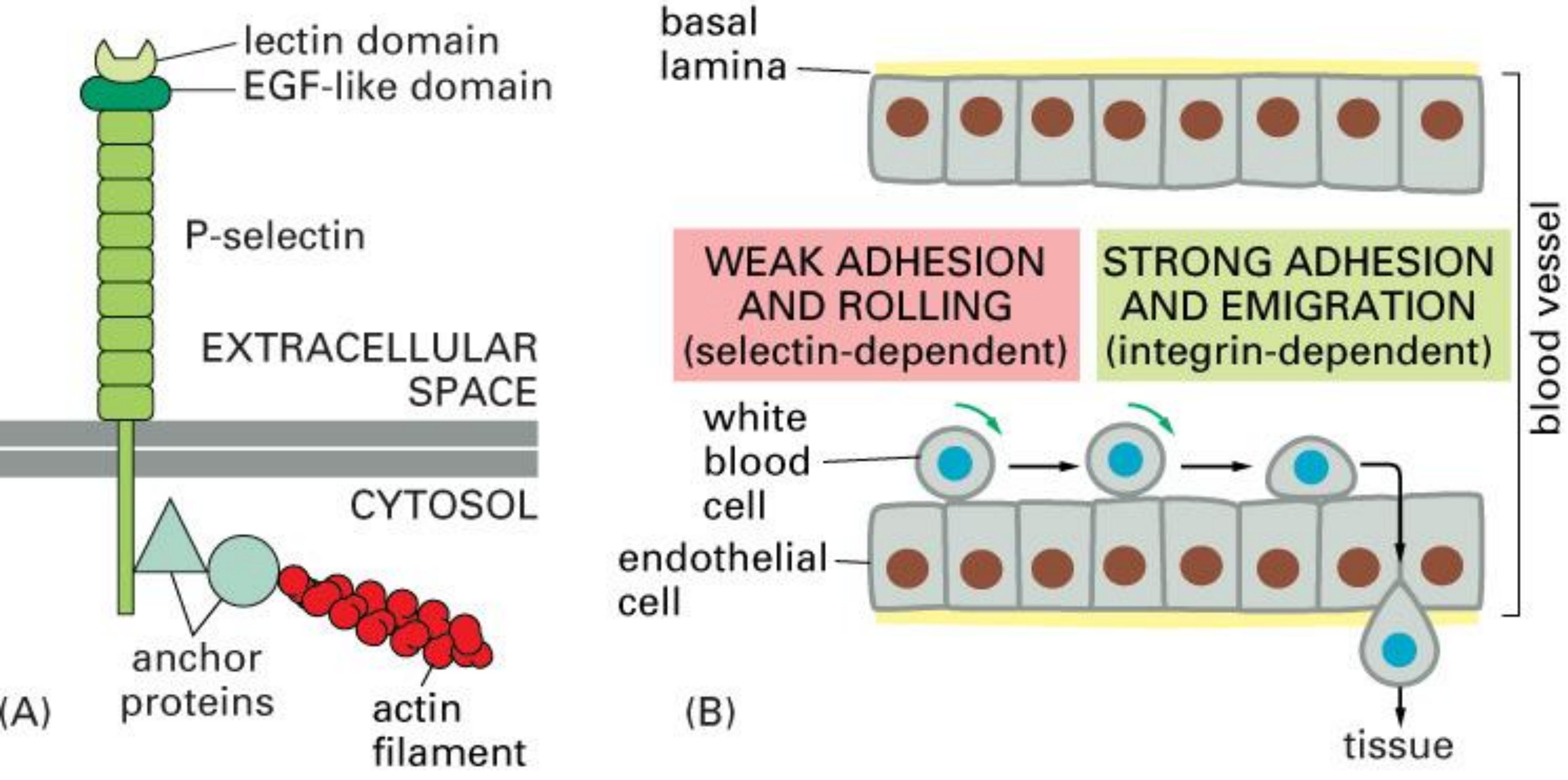
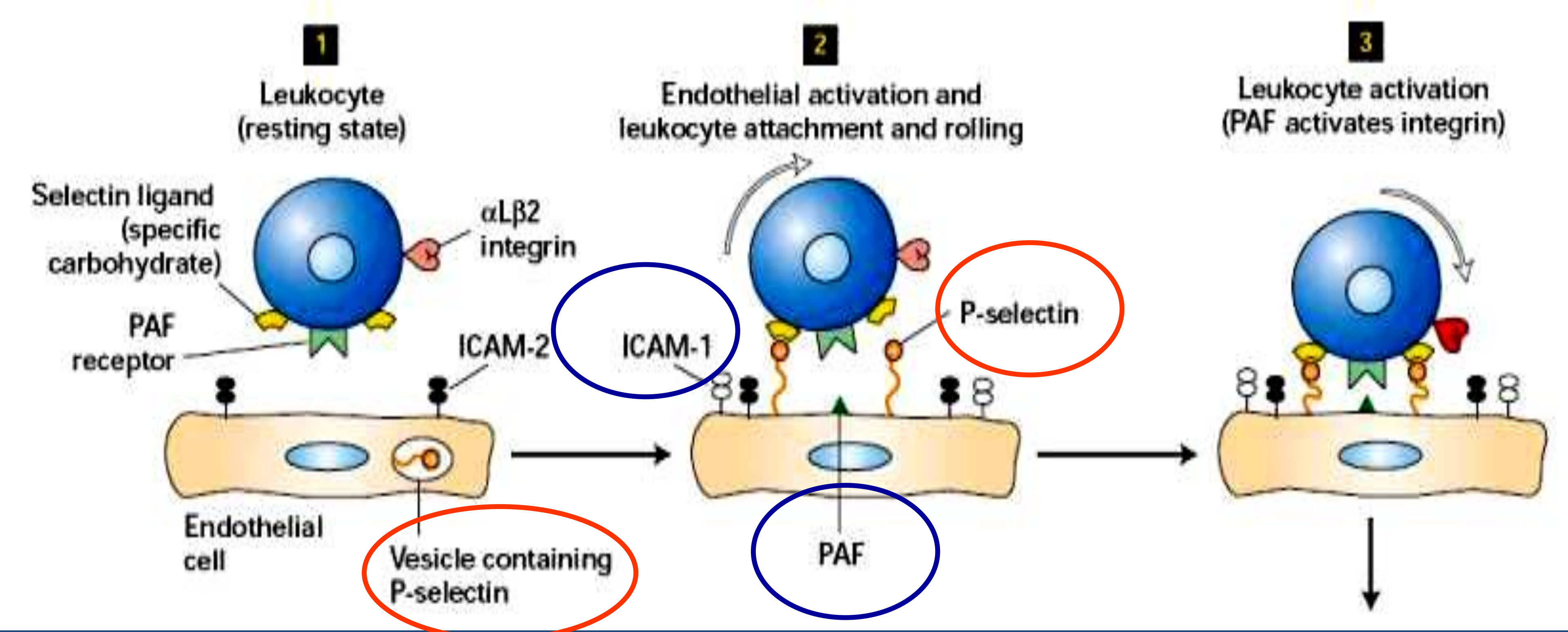


Figure 19–30. Molecular Biology of the Cell, 4th Edition.

The Process of Leukocytes Extravasation


1
Leukocyte (resting state)
2
Endothelial activation and leukocyte attachment and rolling
3
Leukocyte activation (PAF activates integrin)
Selectin ligand (specific carbohydrate)
αLβ2 integrin
PAF receptor
ICAM-2
ICAM-1
P-selectin
Endothelial cell
Vesicle containing P-selectin
PAF

2. Inflammatory signals released -> activation

- moving **selectins** to the cell surface.
  - ◆ Selectins mediate loose binding of leukocytes

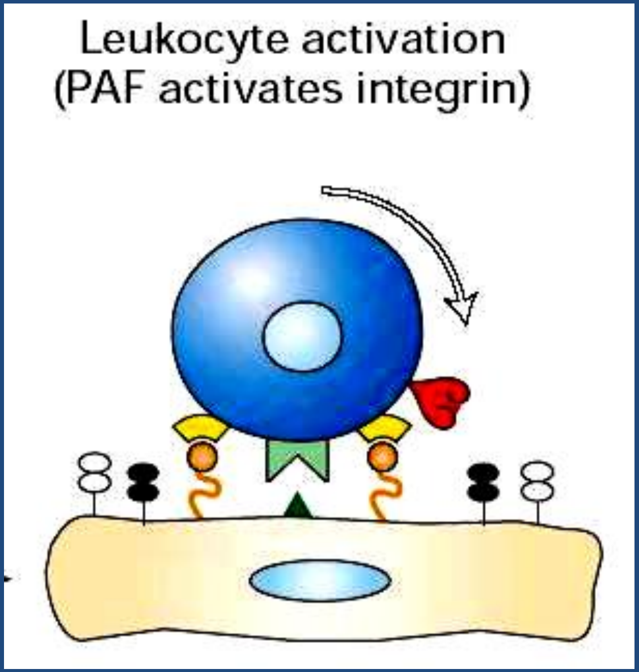
- synthesis of platelet-activating factor (**PAF**) and ICAM-1 (intercellular adhesion molecule)

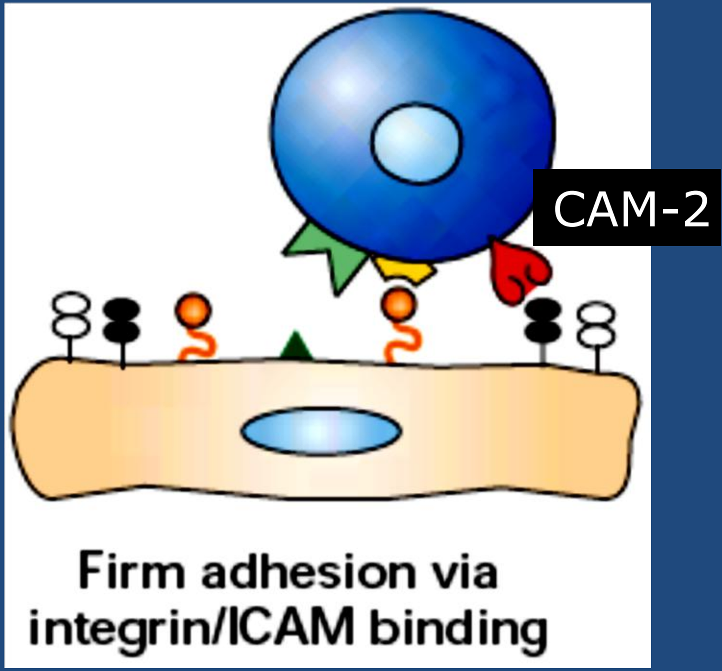
3. Leukocyte activation:

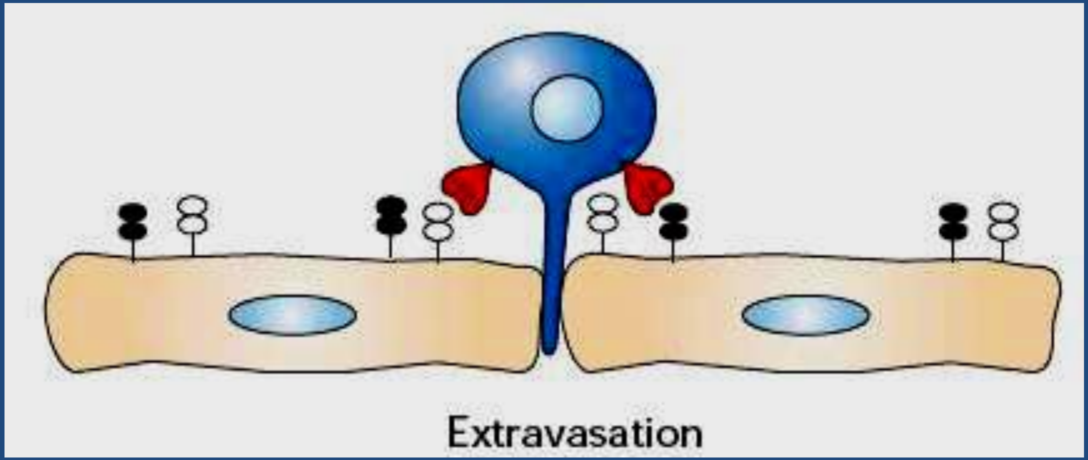
- **Integrins** activation

4. Firm adhesion :

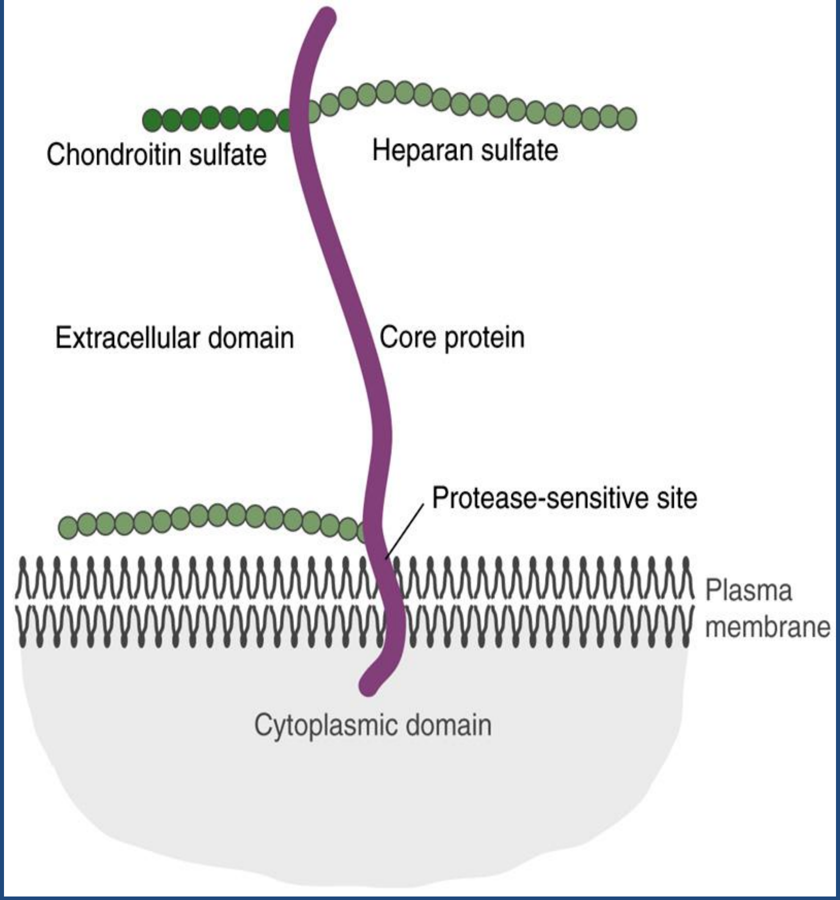
- The tight binding between activated **integrins** on leukocytes and **CAMs** on the endothelium → **extravasation**







Cell surface proteoglycans also link cells to ECM



Syndecan is a common proteoglycan

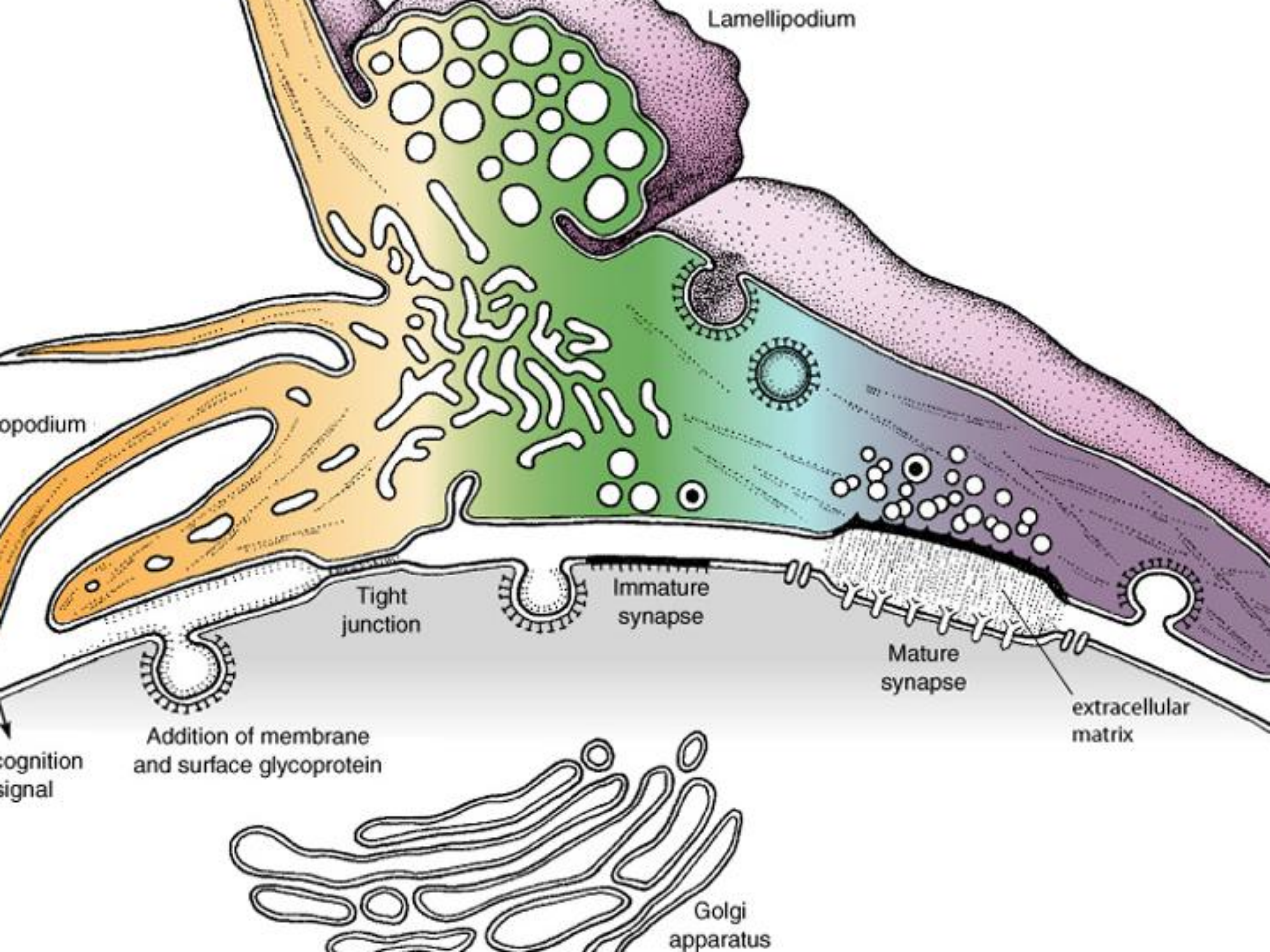
These molecules often have an extracellular and intracellular domain.

Proteoglycans consist of glycosaminoglycans linked to a core protein in the extracellular domain.

These interact with collagen, fibronectin, and other ECM molecules.

Proteoglycans can be released from the cell by cleavage at protease sensitive sites.

Proteoglycans and integrins have another important function:
They are receptors that transduce signals from the extracellular matrix to the nucleus.


Lamellipodium
opodium
Tight
junction
Immature
synapse
Mature
synapse
extracellular
matrix
Addition of membrane
and surface glycoprotein
cognition
signal
Golgi
apparatus